IN THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

Docket Nos. 18-2012, 18-2225, 18-2249, 18-2253, 18-2281, 18-2332, 18-2416, 18-2417, 18-2418, 18-2419, 18-2422, 18-2650, 18-2651, 18-2661, 18-2724, and 19-1385

In re National Football League Players' Concussion Injury Litigation

JOINT APPENDIX Volume VI of XIII, Pages JA3003-JA3970

On appeal from Orders of the United States District Court for the Eastern District of Pennsylvania (Hon. Anita B. Brody), in No. 2:14-md-02323-AB and MDL No. 2323

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UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated,

Plaintiffs,

V.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cv-00029-AB

OBJECTION OF SEAN MOREY, ALAN FANECA, BEN HAMILTON, ROBERT ROYAL, RODERICK "ROCK" CARTWRIGHT, JEFF ROHRER, AND SEAN CONSIDINE TO CLASS ACTION SETTLEMENT

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INTRODUCTION

Objectors agree that "the interests of all parties would be best served by a negotiated resolution of this case." Dkt. No. 5235. Many class members suffer from seriously debilitating injuries in need of immediate medical intervention. Sadly, those injuries affect not only those former players but also their wives, girlfriends, and others around them. Moreover, Defendants' significant misconduct — as alleged in the Class Complaint and trumpeted by Co-Lead Class Counsel early in the case — should not go unaddressed. Yet a settlement that forever adjudicates the rights of thousands of absent class members must be both substantively and procedurally fair, adequate, and reasonable. This Settlement is not, and it should be rejected.

A fair settlement is a compromise with each side giving and getting. But here, the real benefits run to the NFL, which gets a near-absolute release without providing adequate and reasonable compensation in return, and to Class Counsel, who get an extraordinary fee as part of the process. A settlement under these terms is no compromise. It is capitulation.

The Settlement's defects can be fairly summarized as follows:

A lack of adequate representation. The rights of a significant percentage of class members were bargained away without representation by a representative class member or counsel, and the Settlement fails to provide structural assurance of due process protections to all class members. The Settlement includes three conflicts of interest that clearly violate Federal Rule of Civil Procedure 23(a)(4) and the Supreme Court's holding in Amchem Products, Inc. v. Windsor, 521 U.S. 591 (1997): (1) the failure to compensate chronic traumatic encephalopathy (CTE) in those who suffer or die after July 7, 2014; (2) the 75% offsets for non-NFL experienced traumatic brain injuries and strokes; and (3) the failure to credit time played in NFL Europe.

A failure to compensate core class injuries. Co-Lead Class Counsel have rightly proclaimed that "CTE is believed to be the most serious and harmful disease that results from

NFL and concussions."¹ "Thousands of football players, many of whom are thought to have suffered more than one hundred mild traumatic brain injuries, are dealing with horrible and debilitating symptoms."² There is little co-morbidity among CTE and the other diseases compensated in the Settlement. In other words, players can have CTE without having the other diseases. Yet the Settlement provides a \$4 million payment for death with CTE before July 7, 2014, but nothing for players suffering from – or even dying from – CTE after that date. Nor does the Settlement compensate other maladies – including unprovoked seizures and depression – caused by head injuries class members suffered while playing in the NFL.

A lack of proper notice. The slickly packaged notice fails to fairly inform class members of their rights in "plain, easily understood language." Fed. R. Civ. P. 23(c)(2)(B). The notice is misleading at its best, and outright false at its worst. And Class Counsel and their colleagues

Frequent brain trauma or multiple football concussions . . . has shown to cause serious mental health problems. Thousands of football players, many of whom are thought to have suffered more than one hundred mild traumatic brain injuries, are dealing with horrible and debilitating symptoms.

Multiple medical studies have found direct correlation between football concussions and suffering from symptoms of chronic traumatic encephalopathy, also known as CTE. *CTE is believed to be the most serious and harmful disease that results from NFL and concussions.* CTE is a progressive degenerative disease that causes damage to the brain tissue and the accumulation of Tau Proteins.

Up-To-Date Information on NFL Concussions, Seeger Weiss LLP, (Sept. 9, 2014), http://www.seegerweiss.com/football-concussions/#ixzz3CByVHxui (emphasis added) (attached as Exhibit 1) (all exhibit references refer to exhibits attached to the Declaration of Eric R. Nitz). Seeger Weiss quickly removed that language after oral argument in the Third Circuit on September 10, 2014, at which the inadequate representation and failure to compensate CTE, as well as this language on their website, was raised.

¹ Co-Lead Class Counsel Seeger Weiss used to have on its website a tutorial relating to MTBI and football:

 $^{^{2}}$ Id.

have compounded the problem with an aggressive propaganda campaign – laced with misinformation – urging players to accept the settlement.

An unnecessarily complex and confusing claims process. The claims administration process establishes what is essentially an opt-in class, with players required to register within 180 days or forfeit any benefits. Once registered, class members — many of whom are neurocognitively and economically challenged — face a complex and ill-defined process that includes undergoing unreasonable and burdensome testing as well as unlimited appeals at no cost to the NFL but a \$1,000 fee for appeals by class members. The inevitable effect and undeniable intent is to limit claims paid.

A failure to use appropriate testing to determine qualifications for compensation. The Settlement's evaluative testing is not appropriate for determining whether retired professional football players have brain damage, neurodegenerative diseases, or neurocognitive diseases. Rather, it is appropriate only in evaluating younger individuals. Further, the Settlement requires an unrealistically high level of cognitive impairment that would leave many class members with documented cognitive deficits without compensation.

A failure to demonstrate the other indicia required for a fair, adequate, and reasonable settlement. The Third Circuit has articulated a series of factors to be considered in determining whether a class settlement should be approved. See Girsh v. Jepson, 521 F.2d 153, 157 (3d Cir. 1975). The Settlement falls flat when those factors are considered. For example: there was no formal discovery; the NFL can withstand a far greater judgment than what will be paid; the reaction of the class has been understandably negative; and the risks of establishing liability and attendant damages are not high.

In sum, the Settlement is legally defective and plainly unfair. Approval should be denied.

BACKGROUND

I. Procedural History

A. Initial Litigation

In 2011, retired NFL players and their families began suing the NFL, alleging that the NFL breached its duty to protect the health and safety of players and actively misled them about the risks of repeated mild traumatic brain injuries (MTBI). Dkt. No. 6073-5. In 2012, the Judicial Panel on Multidistrict Litigation consolidated these cases in the Eastern District of Pennsylvania. Dkt. No. 1. The NFL Defendants moved to dismiss the complaints on file on preemption grounds, and the Court heard argument on those motions on April 9, 2013. Dkt. Nos. 3590, 4737, 4738. On July 8, 2013, the Court ordered the parties to mediation, which occurred that month. Dkt. No. 5128.

B. The January 6, 2014 Class Action Complaint and Initial Settlement

In August 2013, the court-appointed mediator informed the Court that Class Counsel and NFL Defendants would globally settle all claims arising from the NFL's fraudulent and misleading conduct relating to the effects of MTBI. *See* Dkt. No. 5235. In an August 2013 press release announcing the broad terms of the settlement – issued five months before the Complaint was filed – the mediator stated that the settlement called for a \$675 million fund to "compensate former players who have suffered cognitive injury or their families," among other terms. Press Release, *NFL*, *Retired Players Resolve Concussion Litigation*, Irell & Manella LLP, http://static.nfl.com/static/content/public/photo/2013/08/29/0ap2000000235504.pdf (attached as Exhibit 2). The fund was to compensate "severe cognitive impairment, dementia, Alzheimer's, [and] ALS." *Id.* "The precise amount of compensation," the mediator stated, "will be based upon the specific diagnosis, as well as other factors including age, number of seasons played in the NFL, and other relevant medical conditions." *Id.* On January 6, 2014, Class Counsel for the

first time publicly revealed the specific terms of the settlement when they filed their Class Action Complaint, settlement agreement, and first motion for preliminary approval. *See* Dkt. No. 5634.

1. The Class Action Complaint

The Class Action Complaint defines a class consisting of all living, retired NFL Football Players who have retired from the NFL before preliminary approval of the proposed settlement agreement as well as representatives of retired NFL players who have died or become legally incapacitated. *See Turner v. Nat'l Football League*, Civ. A. No. 2:14-cv-29-AB, Dkt. No. 1 ¶¶ 1, 16 (E.D. Pa. Jan. 6, 2014) ("Complaint," or "Compl."). It further defines NFL Football Players to include not just players in the NFL and its member clubs but also players in the American Football League, which merged with the NFL, the NFL Europe League, and the World League of American Football. *Id.* ¶ 1. The class also includes spouses, parents, dependent children, and any other person who under state law may sue the NFL by virtue of his or her relationship with the retired player. *Id.*

The Complaint divides the class into two sub-classes. Subclass 1 consists of all retired players (and their representative and derivative claimants) who "were not diagnosed with dementia, Alzheimer's Disease, Parkinson's Disease, ALS and/or Death with CTE prior to the date of the Preliminary Approval and Class Certification Order." Compl. ¶ 17(a). Subclass 2 consists of all retired players (and their representative and derivative claimants) who "were diagnosed with dementia, Alzheimer's Disease, Parkinson's Disease, ALS and/or Death with CTE prior to the date of the Preliminary Approval and Class Certification Order." *Id.* ¶ 17(b). Subclass 2 also includes the representative and derivative claimants of retired players "who died before Preliminary Approval" of the settlement and who "received a post-mortem diagnosis" of Death with CTE. *Id.*

Shawn Wooden and Kevin Turner are the Representative Plaintiffs for the class. Mr. Wooden represents Subclass 1. Compl. ¶ 17(a). A safety, Mr. Wooden played in the NFL from 1996 until 2004 with the Miami Dolphins and the Chicago Bears. *Id.* ¶ 4. He is alleged to have "experienced" unspecified "neurological symptoms" but "has not been diagnosed with any neurocognitive impairment." *Id.* The Complaint states that Mr. Wooden has an "increased risk of developing dementia, Alzheimer's, Parkinson's, or ALS." *Id.* Mr. Turner represents Subclass 2. *Id.* ¶ 17(b). A running back, Mr. Turner played in the NFL from 1992 until 1999 with the New England Patriots and the Philadelphia Eagles. *Id.* ¶ 7. He was diagnosed with ALS in 2010. *Id. Neither Mr. Wooden nor Mr. Turner alleges that he suffers from CTE or faces an increased risk of suffering from CTE*.

Although neither Mr. Wooden nor Mr. Turner alleges that he suffers from CTE or faces an increased risk of suffering from CTE, the Complaint identifies several long-term injuries arising from MTBI, "including, but not limited to . . . *CTE and its related symptoms*." Compl. ¶ 127 (emphasis added).

a. The NFL's Duty of Care and the MTBI Committee

The Complaint alleges that the NFL assumed a duty of care to protect its players from the adverse consequences of the repeated head injury they sustained while playing football. Throughout its existence, the NFL received medical advice about the health risks of repeated MTBI, placing it in a superior position of knowledge over the players. Compl. ¶ 70.

The Complaint explains that, by the mid-1990s, the link between repetitive mild head trauma and neurodegenerative disease had been well-established. As early as 1952, the *New England Journal of Medicine* had recommended a three-strike rule for concussions in football, recommending that a player retire after having received his third concussion. Compl. ¶ 95. In

the 1980s, published studies had identified long-term brain damage and unexpected cognitive impairment in patients who had experienced MTBI. *Id.* ¶ 105.

As the Complaint explains, by the mid-1990s, the NFL had begun sponsoring its own medical research into the effect of concussions and repeated head injury on NFL football players. Compl. ¶ 84. It founded the Mild Traumatic Brain Injury Committee (MTBI Committee), which was publicized as independent from the NFL and tasked with studying the effects of brain injury in football players. *Id.* ¶¶ 134-136. Despite promises of independence, the League appointed as chairman Dr. Elliott Pellman, a team doctor and rheumatologist with no clinical or research experience in neurology. *Id.* ¶ 138. The other four members also were affiliated with the NFL. *Id.* ¶ 137. The MTBI Committee was aware of the long line of medical research tying repeated head injury to neurodegenerative disease. Dr. Pellman's eventual successor as chairman, Dr. Ira Casson, stated in written testimony before Congress in January 2010 that he had "been concerned about the possibility of long term effects on the brain related to football for close to thirty years." *Id.* ¶ 209.

b. Criticism of the MTBI Committee

The Complaint alleges that the MTBI Committee's "research" stood in stark contrast to studies previously published. Despite years of contrary research by leading authorities, the *NFL's MTBI Committee* – in its first published paper in 2003 – *concluded that concussions presented no long-term health risk*. Compl. ¶ 147. Between 2003 and 2009, the MTBI Committee published *fifteen more papers*, all of which supported the NFL's position that *concussions presented no long-term adverse risks*. *Id.* ¶ 148. The Complaint cites a 2004 article, for example, that found no risk of repeated concussions in players who had suffered a previous concussion and denied the existence of a "7-to-10 day window of increased susceptibility to sustaining another concussion." *Id.* ¶ 151. In the commentary on that

publication, another physician wrote that the "article sends a message that it is acceptable to return players while still symptomatic, which contradicts literature published over the past twenty years suggesting that athletes be returned to play only after they are asymptomatic, and in some cases for seven days." Id. ¶ 152. Nevertheless, the Committee repeated the conclusion a year later: "Return to play does not involve a significant risk of a second injury either in the same game or during the season." Id. ¶ 153.

As criticism of the MTBI Committee's research grew, the Committee went on the offensive. Researchers who published conclusions contrary to the MTBI Committee's position were attacked. For example, after Dr. William Barr presented NCAA study findings that contradicted NFL practices, Dr. Pellman fired Dr. Barr from his position as a neuropsychologist for the New York Jets. Compl. ¶ 168. And after Dr. Bennet Omalu began identifying cases of CTE in retired football players, the MTBI Committee pressured the journal that published Dr. Omalu's studies to retract them. *Id.* ¶ 173. When one neurosurgeon presented to the MTBI Committee studies linking NFL head injuries with cognitive decline, "[t]he Committee got mad." *Id.* ¶ 193.³ By 2008, Dr. Ann McKee of Boston University had built on Dr. Omalu's work and identified CTE in two more retired football players. *Id.* ¶ 196. The MTBI Committee characterized her work as an "isolated incident" and dismissed it: "[T]here is not enough valid, reliable or objective scientific evidence at present," Dr. Casson argued, "to determine whether ... repeat head impacts in professional football result in long term brain injury." *Id.* ¶ 197.

Even after Dr. Casson and Dr. David Viano replaced Dr. Pellman as chair of the MTBI Committee (Pellman is now the NFL Medical Director), the Committee continued denying the

³ The neurosurgeon further stated that "we got into it. And I'm thinking, 'This is a . . . disease in America's most popular sport and how are its leaders responding? Alienate the scientist who found it? Refuse to accept the science coming from him?'" Compl. ¶ 193.

link between MTBI and brain disease. Compl. ¶¶ 188, 191. For example, in 2007 Dr. Casson unequivocally denied any link between concussions and depression, dementia, Alzheimer's, or "anything like [that] whatsoever." *Id.* ¶ 191.

c. The NFL's Representations About Head Injuries

The NFL relied on the MTBI Committee's heavily criticized research in communicating with its players. For example, as the Complaint alleges, in 2007 the NFL provided each player with a concussion pamphlet stating that "[c]urrent research with professional athletes has not shown that having more than one or two concussions leads to permanent problems if each injury is managed properly. It is important to understand that there is no magic number for how many concussions is too many." Compl. ¶ 180. When the pamphlet was released, Commissioner Roger Goodell issued a statement explaining that he wanted to ensure players "are fully informed and take advantage of the most up to date information and resources as we continue to study the long-term impact on concussions." *Id.* ¶ 181. Nonetheless, the pamphlet did not refer to or cite the numerous studies demonstrating a link between repeated concussions and neurodegenerative brain diseases, such as CTE. *Id.*

The Complaint also describes how, by 2010, the NFL had renamed the MTBI Committee the "Head, Neck, and Spine Medical Committee." Compl. ¶ 213. Dr. Pellman was removed from the Committee and Dr. H. Hunt Batjer and Dr. Richard Ellenbogen were named co-chairs. *Id.* The Head, Neck, and Spine Medical Committee admitted that the MTBI Committee's data was "infected" and should be collected anew. *Id.* ¶ 214. Dr. Batjer even admitted that the MTBI Committee's research was methodologically flawed and was "not acceptable by any modern standards." *Id.* ¶ 216. And when a promotional brochure for a league-sponsored symposium described the concussion crisis as "hype around assertions of long-term harm to players from

head injuries," Dr. Batjer disagreed. "They aren't assertions or hype," he said referring to the scientific evidence of the link between MTBI and long-term brain damage.⁴ "They are facts." 5

In 2011, another member of the Head, Neck, and Spine Medical Committee admitted that the MTBI Committee's previous long-range study had "no science" in it and that the data from that study would not be used in a new study that was underway. Compl. ¶ 222. In recognizing the validity of science suggesting a link between long-term brain damage and concussions, the Head, Neck, and Spine Medical Committee was late to the game, even by NFL standards. Two years earlier, NFL spokesman Greg Aiello had admitted: "It's quite obvious from the medical research that's been done that concussions can lead to long-term problems."

The Complaint notes that, throughout this time period, the NFL fostered a culture where head trauma, "dings," and "getting your bell rung" were considered badges of honor. For example, the NFL glorified – and profited handsomely from – players' most violent hits. It created a series of videos through NFL Films that featured in slow motion the League's most aggressive and violent plays. Compl. ¶¶ 41-42, 47. Among the names of these films: *Big Blocks and King Size Hits, The Best of Thunder and Destruction – NFL's Hardest Hits, Crunch Course, Crunch Course II, The NFL's Greatest Hits,* and *Moment of Impact. Id.* ¶ 43.

2. The Initial Settlement

Notwithstanding the breadth of afflictions linked to MTBI, the initial settlement compensated only a limited number of diseases and limited total class-wide compensation for

⁴ Schwarz, *Concussion Committee Breaks with Predecessor*, N.Y. Times (June 1, 2010), http://www.nytimes.com/2010/06/02/sports/football/02concussion.html (attached as Exhibit 3).

⁵ *Id*.

⁶ Schwarz, *N.F.L. Acknowledges Long-Term Concussion Effects*, N.Y. Times (Dec. 20, 2009), http://www.nytimes.com/2009/12/21/sports/football/21concussions.html?_r=0 (attached as Exhibit 4).

those injuries to \$675 million. See Dkt. No. 5634-2 §§ 23.1-23.5. ALS claimants were to receive a maximum award of \$5 million. See id. at Ex. 3. Retired players diagnosed with Parkinson's Disease or Alzheimer's Disease were to receive a maximum \$3.5 million award. Id. And class members exhibiting Level 2 or Level 1.5 dementia were to receive at most \$3 million or \$1.5 million, respectively. Id. The full written initial settlement also revealed that – contrary to previous public statements from Co-Lead Class Counsel – it would compensate cases of CTE with a maximum \$4 million award only if the retired player died before preliminary approval of the settlement. See Dkt. No. 5634-2 §§ 2.1(xxx), 6.3 & Ex. 1 ¶ 5. Players suffering from CTE who would be diagnosed or died after that date were to receive nothing. Moreover, players suffering from the mood and behavioral symptoms of CTE were to receive no compensation under the settlement unless they independently qualified for compensation through one of the other qualifying diagnoses. Id. § 6.3.

The initial settlement also created a Baseline Assessment Program ("BAP") that would have provided class members the opportunity to undergo a baseline assessment examination, which would establish the class member's baseline neurocognitive functioning and screen for dementia and neurocognitive impairment. Dkt. 5634-2 § 5.2. Class members who were diagnosed with Level 1 dementia in the baseline assessment examination would be entitled to supplemental benefits that would cover the costs of medical treatments related to the dementia. *Id.* §§ 5.2, 5.11. The term of the BAP was to be ten years, but class members receiving supplemental benefits would continue to do so for up to five years beyond that ten-year term. *Id.* §§ 5.5, 5.11. The initial settlement capped the BAP Fund at \$75 million. *Id.* § 23.3(g).

⁷ Calling it a \$675 million fund was not accurate. It was a \$300 million fund paid over two years, with another \$375 million paid over 17 years. *See* Dkt. No. 5634-2 §§ 23.1-23.5.

On January 14, 2014, this Court, *sua sponte*, denied Class Counsel's motion for preliminary approval of the settlement. *In re Nat'l Football League Players' Concussion Injury Litig.*, 961 F. Supp. 2d 708 (E.D. Pa. 2014). The Court recognized that the "Monetary Award Fund may lack the necessary funds to pay Monetary Awards for Qualifying Diagnoses" and "[a]s a first step toward preliminary approval" "order[ed] the parties to share the [actuarial and economic] documentation" relied upon during settlement "with the Court through the Special Master." *Id.* at 715-16.

C. Objectors' Motion To Intervene

Objectors moved to intervene. See Dkt. No. 6019. They explained that their interests were not adequately represented during the negotiation of the initial settlement, in part because that settlement arbitrarily denied compensation to individuals whose CTE went undetected until after preliminary approval. Because each Objector exhibits MTBI-related conditions that are also symptoms of CTE, each is at risk of developing CTE. Even though the settlement would have awarded \$4 million to the families of players who died with CTE before final approval of the settlement, Objectors and their families would receive nothing if later diagnosed with CTE. Id. at 13-18. In opposing the motion to intervene, Class Counsel ignored this fact entirely, offering no explanation for the disparate treatment of CTE claimants. See Dkt. No. 6046. Objectors also criticized the 75% offset imposed on any player who suffers a *single* stroke or a single instance of non-football related traumatic brain injury ("TBI"). Dkt. 5634-2 § 6.5(b)(ii)-(iii). Such a player would recover only 25% of what he is otherwise entitled to receive under the settlement. Again, Class Counsel's opposition was devoid of any explanation for this offset. See Dkt. No. 6046. Objectors noted other defects in the initial settlement and other class members voiced criticism as well. See, e.g., Dkt. Nos. 5686, 5771.

D. The Revised Settlement

Notwithstanding those criticisms of the initial settlement, Class Counsel on June 25, 2014 submitted a revised settlement agreement that retained the same structure and almost all of the key provisions of the initial settlement. *See* Dkt. No. 6073-2 ("Settlement"). Class Counsel moved for "conditional" class certification and preliminary approval of the Revised Settlement. *See* Dkt. No. 6073.

1. Compensation

Like the initial settlement, the Settlement compensates only the same limited subset of the diseases that have been linked to MTBI: ALS, Parkinson's, Alzheimer's, Level 2 dementia, and Level 1.5 dementia. Settlement Ex. B-3. It also retains the maximum compensation awards provided for each of these diseases in the initial settlement. *Id.* Similar to the initial settlement, the Settlement compensates cases of CTE with \$4 million, but *only if the claimant dies before preliminary approval of the settlement agreement.* Settlement §§ 2.1(yyy), 6.2(a) (providing compensation for a "Qualifying Diagnosis"); *id.* Ex. B-1 at 5.8 Unlike its predecessor, the Settlement does not cap total compensation for ALS, Parkinson's, Alzheimer's, and Levels 1.5 and 2 dementia, but it retains the \$75 million cap on the BAP Fund. *See* Dkt. 6073-5 at 4.

The Settlement still has a series of offsets that reduce a claimant's compensation. Most notably, the Settlement retains the 75% offset for a single stroke or a single non-football related TBI – and an offset that is compounded if a class member suffers both. Settlement §§ 6.7(b)(ii)-(iii), (e). Additionally, class members who played fewer "Eligible Seasons" in the NFL receive

⁸ Section 6.2(a) of the Settlement provides compensation for any "Qualifying Diagnosis." Section 2.1(yyy) defines "Qualifying Diagnosis" to include "Death with CTE." Exhibit B-1 defines "Death with CTE" as follows: "For Retired NFL Football Players *who died prior to the date of the Preliminary Approval and Class Certification Order*, a post-mortem diagnosis of CTE made by a board-certified neuropathologist." Settlement Ex. B-1 at 5 (emphasis added).

only a percentage of the maximum award for their condition. *See* Settlement § 6.7(b)(i). Although class members receive "Eligible Season" credit for service on "practice, developmental, or taxi squad[s]," time spent playing for NFL Europe or its related leagues does not apply to the "Eligible Season" determination. *Id.* §§ 2.1(kk), 6.7(c)(1). Similarly, class members who are older at the time of the Qualifying Diagnosis receive only a percentage of the maximum award for their condition. *See id.* § 6.7(b) & Ex. B-3.

2. Eligibility

A complex series of administrative procedures governs the distribution of benefits. Class members must register with the Claims Administrator within 180 days of Settlement Class Supplemental Notice. Settlement § 4.2(c). Failure to do so renders the player *completely ineligible* for any benefits, yet the release would be binding. *Id.* Additionally, the undiagnosed players in Subclass 1 must undergo the baseline assessment examination to receive the full award; failure to undergo the examination results in a 10% reduction in benefit. *Id.* §§ 5.4, 6.7(b)(iv). The Baseline Assessment Program itself imposes a series of deadlines. Players aged 43 and older must obtain the BAP examination within two years after the BAP commences; younger players must do so by the earlier of their 45th birthday or the BAP's tenth year. *Id.* § 5.3.

The BAP requires players to participate in neuropsychological tests that do not evaluate the relevant neurodegenerative diseases for purposes of determining relief. For example, instead of targeting the neurodegenerative diseases of CTE or Alzheimer's, the tests are designed for younger traumatic brain injury patients. *See* Decl. of Robert A. Stern ("Stern Decl.") ¶ 43. Moreover, the tests are not consistent with the neuropsychological tests typically employed by doctors to evaluate patients for mild cognitive impairment or Alzheimer's disease dementia. *Id.* ¶¶ 43-46.

The tests also do not determine whether a former player suffers from the specific types of behavioral and mood disorders affiliated with a history of head trauma, including aggression, impulsivity, or dementia. Stern Decl. ¶¶ 31, 45. Not only are these tests entirely inappropriate for purposes of identifying the compensable neurodegenerative diseases under the Settlement, but the manner and timing in which they are administrated will produce inaccurate results. *Id.* ¶¶ 44-46. If a patient has a disease at the level of severity required for compensation, the length and complexity of testing to which he must submit himself is far too long; indeed, the extra tests only increase the likelihood that a patient will not be able to complete the exam. *Id.* ¶ 44. In short, the Settlement requires players to submit to the wrong medical tests with unfairly high evaluation bars that by no means ensure proper or accurate medical evaluations.

Both the NFL and claimants may appeal adverse claim determinations. Settlement §§ 9.5-9.7. The initial settlement limited the NFL to ten appeals per year, but the Settlement allows unlimited appeals by the NFL. *Compare* Dkt. No. 5634-2 § 9.6(b) *with* Settlement § 9.6(b). Claimants – but not the NFL – must pay a \$1,000 fee to docket an appeal. Settlement § 9.6(a). The fee is refunded if the appeal is successful. *Id*.

3. The Release

The Settlement broadly releases all MTBI-related claims of every class member who does not opt out, including claims of class members who played in NFL Europe and its predecessors. Class members:

waive and release . . . any and all past, present and future claims, counterclaims, actions, rights or causes of action . . . in law or in equity . . . known or unknown, suspected or unsuspected, foreseen or unforeseen, matured or unmatured, accrued or unaccrued, liquidated or unliquidated [that any settling plaintiff] had, has, or may have in the future arising out of, in any way relating to or in connection with the allegations, transactions, facts, matters, occurrences, representations or omissions involved, set forth, referred to or relating to the Class Action Complaint and/or Related Lawsuits

Settlement § 18.1(a). The Settlement states that the claims it releases include, among others, claims "arising out of, or relating to . . . head, brain and/or cognitive injury, as well as any injuries arising out of, or relating to, concussions and/or subconcussive events . . . of whatever cause" and claims "arising out of, or relating to, CTE." *Id.* § 18.1(a)(ii), (iv). The Settlement's release also requires class members to acknowledge that they "explicitly took unknown or unsuspected claims into account in entering into the Settlement Agreement and it is the intention of the Parties fully, finally and forever to settle and release all Claims" falling within the scope of the allegations in the Complaint and related lawsuits. *Id.* § 18.2.

4. Attorneys' Fees

The Settlement calls for a \$112.5 million attorneys' fee to be paid within 60 days after the Settlement is final, which the NFL Defendants have agreed not to oppose. Settlement §§ 21.1-.2.9 It also authorizes Co-Lead Class Counsel to "petition the Court to set aside up to five percent (5%) of each Monetary Award . . . to facilitate the Settlement program and related efforts of Class Counsel." *Id.* The initial settlement did not contain this set-aside provision. *Compare id. with* Dkt. No. 5634-2 § 21.1. The Settlement places no limits on how Co-Lead Class Counsel may use the set aside.

E. Opposition to Preliminary Approval

One week after Class Counsel moved for preliminary approval, Objectors filed an objection to the settlement and opposed the motion for preliminary approval. They argued, among other things, that intra-class conflicts precluded certification under Rule 23(a)(4). Dkt.

⁹ The NFL Defendants have taken no position on the propriety of the fee award, noting that "any such proposed set aside application is a matter strictly between and among Settlement Class Members, Class Counsel, and individual counsel for Settlement Class Members." Settlement § 21.1.

No. 6082 at 19-29. Most notably, class members suffering from CTE would receive no compensation after preliminary approval but those who died before approval would receive up to \$4 million. *Id.* at 20-26. Objectors also challenged the proposed notice because it falsely indicated that the settlement compensated future cases of CTE. *Id.* at 29-32. And Objectors objected to the labyrinth of procedural requirements for obtaining relief, which would likely prevent many class members from recovering. *Id.* at 32-35.

F. Preliminary Approval

On July 7, 2014, this Court certified the class for settlement only, preliminarily approved the Settlement, established an opt-out/objection procedure, and scheduled a fairness hearing. Dkt. Nos. 6083, 6084. Objectors petitioned to appeal the class certification decision under Rule 23(f), and the Third Circuit denied that petition on September 11, 2014. Dkt. No. 6166.

II. Background of Objectors

Sean Morey, Alan Faneca, Ben Hamilton, Robert Royal, Roderick Cartwright, Jeff Rohrer, and Sean Considine are all class members and NFL veterans; one also played in NFL Europe. They played, on average, eight years in the league, and most received NFL-administered injections of Toradol, a pain-killer. They are collegiate All-Americans, team captains, Pro-Bowlers, and Super Bowl Champions. *See* Dkt. No. 6082 at 2-5. A more extensive statement of the Objectors' background is included as Appendix A to this Objection.

Since leaving the NFL, Objectors have experienced one or more of a wide range of symptoms linked to repetitive mild traumatic brain injury (MTBI), including a sensitivity to noise, visuospatial issues, visual impairment, chronic pain, executive function deficit, episodic depression, mood and personality changes, chronic headaches, dysnomia, a decreased ability to multi-task, peripheral nerve dysfunction (numbness, burning, and/or tingling), cervical spinal disorders, sleep dysfunction, attention and concentration deficits, short- and long-term memory

deficits, and somatic disorders. Additionally, some of the Objectors also have experienced a decreased ability to interpret, regulate, express, or control complex emotions. These conditions have been associated with CTE and may broaden or intensify as time passes.

Although the Objectors' claims for their injuries would be released by the Settlement, it appears that none would qualify for any relief under the settlement beyond participation in the Baseline Assessment Program ("BAP"). And the BAP – which measures cognitive deficits such as memory impairment and loss of attention – does not even screen for many of the Objectors' common neurobehavioral conditions or neuropsychiatric presentations.

ARGUMENT

This Court has a "fiduciary responsibility as the guardian of the rights of the absentee class members." *Girsh v. Jepson*, 521 F.3d 153, 157 (3d Cir. 1975); *see also In re Pet Food Prods. Liab. Litig.*, 629 F.3d 333, 351 (3d Cir. 2010) ("Rule 23(e) places a duty on district courts to safeguard the interests of class members"). That responsibility arises because class actions present the unique circumstance where class counsel have "the incentive . . . , in complicity with the defendant's counsel, to sell out the class by agreeing with the defendant to recommend that the judge approve a settlement involving a meager recovery for the class but generous compensation for the lawyers." *Eubank v. Pella Corp.*, 753 F.3d 718, 720 (7th Cir. 2014).

Courts must "be even more scrupulous than usual in approving settlements where no class has yet been formally certified." *In re Gen. Motors Corp. Pick-Up Truck Fuel Tank Prods. Liab. Litig.*, 55 F.3d 768, 805 (3d Cir. 1995) ("*GM Trucks*"). Such caution is necessary because "the 'danger of a premature, even a collusive, settlement [is] increased when . . . the status of the action as a class action is not determined until a settlement has been negotiated, with all the momentum that a settlement agreement generates.'" *Id.* at 788 (quoting *Mars Steel Corp. v. Cont'l Ill. Nat'l Bank & Trust Co.*, 834 F.2d 677, 680 (7th Cir. 1987)).

"Pre-certification negotiations also hamper a court's ability to review the true value of the settlement or the legal services after the fact," and "deny[] other plaintiffs' counsel information that is necessary for them to make an effective evaluation of the fairness of any settlement that results." *GM Trucks*, 55 F.3d at 788. And "where notice of the class action is ... sent simultaneously with the notice of the settlement itself, the class members are presented with what looks like a fait accompli." *Mars Steel*, 834 F.2d at 680-81. As a result, "even if [class members] have enough information to conclude the settlement is insufficient and unsatisfactory, the mere presentation of the settlement notice with the class notice may pressure even skeptical class members to accept the settlement out of the belief that . . . they really have no choice." *GM Trucks*, 55 F.3d at 789.

In short, the need for the Court's guardianship of absentee class members is particularly acute where, as here, a class settlement is negotiated before certification. The Court's exercise of that guardianship includes an assessment of the adequacy of class representation under Federal Rule of Civil Procedure 23(a)(4). *See Amchem*, 521 U.S. at 621; *GM Trucks*, 55 F.3d at 794 (denying approval of settlement where class not certifiable for lack of adequate representation). If the settlement terms create "'adversity among subgroups[,]... the members of each subgroup cannot be bound to a settlement except by consents given by those who understand that their role is to represent solely the members of their respective subgroups.'" *Amchem*, 521 U.S. at 627. In the presence of such intra-class conflicts, the settlement requires the "structural assurance of fair and adequate representation." *Id.* The Court must also consider whether the settlement provides "the best notice that is practicable under the circumstances." Fed. R. Civ. P. 23(c)(2)(B). A false or misleading notice does not "clearly and concisely state in plain, easily understood language... the nature of the action[,] the definition of the class certified[, and] the class claims,

issues, or defenses." *Id.* Finally, the Court must determine that the settlement "is fair, reasonable, and adequate." Fed. R. Civ. P. 23(e). The settling parties must carry the burden of proving that these requirements are met. *See GM Trucks*, 55 F.3d at 785.

I. The Lack of Adequate Representation Precludes Certification

A fair settlement requires a certifiable class with the interests of all class members adequately represented. GM Trucks, 55 F.3d at 784. Rule 23 demands that "the representative parties will fairly and adequately protect the interests of the class." Fed. R. Civ. P. 23(a)(4). The proposed class fails this requirement. The "linchpin of the adequacy requirement is the alignment of interests and incentives between the representative plaintiffs and the rest of the class." Dewey v. Volkswagen Aktiengesellschaft, 681 F.3d 170, 183, 187-88 (3d Cir. 2012) (denying preliminary class certification where interests of representative plaintiffs and absent class members diverged). When assessing the adequacy of representation, "a judge must focus on the settlement's distribution terms (or those sought) to detect situations where some class members' interests diverge from those of others in the class." GM Trucks, 55 F.3d at 797 (representation inadequate where settlement terms preferred some class members over others). Thus, "a settlement that offers considerably more value to one class of plaintiffs than to another may be trading the claims of the latter group away in order to enrich the former group." Id. Offering considerably more value to one class of plaintiffs is precisely what the Settlement does here.

The lack of adequate representation here has manifested itself primarily through three intra-class conflicts. *First*, the Settlement arbitrarily limits compensation for CTE to individuals who died before preliminary approval of the Settlement. Class members whose CTE is discovered in the future receive nothing. *Second*, the Settlement reduces a claimant's award by 75% if (i) the claimant has suffered a stroke, even though the NFL Defendants' own conduct in

administering Toradol increased some Objectors' risk of stroke, or (ii) the claimant has suffered a *single* non-football related TBI, even though one TBI is dwarfed by the dozens of diagnosed and undiagnosed TBIs that the retired NFL player received while playing in the NFL. *Third*, the settlement class includes veterans of NFL Europe, but the Settlement does not credit seasons played in that league as "eligible seasons."

A. The Failure-To-Compensate-CTE Conflict Demonstrates Lack of Adequate Representation

The greatest of the Settlement's many flaws is its failure to compensate players who are living with CTE or who die with it after July 7, 2014 – notwithstanding that the family of a player who died with CTE before July 7, 2014 receives \$4 million. Medical evidence demonstrates that CTE is likely to be far and away the most common neurocognitive disease suffered by the class. *Neither class representative alleges that he has CTE or is at increased risk of developing CTE*. Yet all class members release their claims related to CTE. They receive nothing but the right to participate in the BAP – with its ill-defined benefits and \$75 million total cap.

Class Counsel bargained away the rights of more than 20,000 former NFL players – many of whom are suffering the serious effects of CTE, fairly called "football's industrial disease." This alone is reason to reject the settlement.

1. Chronic Traumatic Encephalopathy (CTE)

"CTE is a unique neurodegenerative condition that is associated with repetitive mild traumatic brain injury." CTE has been found in football players, boxers, hockey players,

¹⁰ McKee *et al.*, *The Spectrum of Disease in Chronic Traumatic Encephalopathy*, 136 Brain 43, 62 (2013) ("McKee *et al.* 2013") (attached as Exhibit 5); *see also, e.g.*, Jordan, *The Clinical Spectrum of Sport-Related Traumatic Brain Injury*, 9 Nature Reviews Neurology 222, 225 (2013) ("CTE is the long-term neurological consequence of repetitive mild TBI.") (attached as

military veterans exposed to explosions, and domestic violence victims.¹¹ It is "a distinct neurodegeneration" disease different from, for example, Alzheimer's, Parkinson's, or ALS.¹² It "is the only known neurodegenerative dementia" caused specifically by repetitive head trauma.¹³ Thus, of the diseases addressed in the Settlement, it is the only one that occurs *only* by being hit in the head.

CTE's neuropsychological and neuropsychiatric effects typically fall into one of three categories: mood/behavioral, motor, and cognitive.¹⁴ Researchers have identified four stages of CTE.¹⁵ Stage I symptoms include headache, loss of attention and concentration, short-term memory difficulties, aggression, depression, executive dysfunction, and explosivity.¹⁶ Stage II

Exhibit 6); Saulle & Greenwald, *Chronic Traumatic Encephalopathy: A Review*, Rehabilitation Research & Practice 2 (2012) ("It has been well established that repetitive concussive or subconcussive blows to the head place individuals at risk for CTE."), http://www.hindawi.com/journals/rerp/2012/816069/ (attached as Exhibit 7).

¹¹ Mitsis et al., Tauopathy PET and Amyloid PET in the Diagnosis of Chronic Traumatic Encephalopathies, 4 Translational Psychiatry 1, 1 (2014) (attached as Exhibit 8).

Baugh et al., Current Understanding of Chronic Traumatic Encephalopathy, 16 Current Treatment Options in Neurology 306, at 1/13 (2014) ("Baugh et al. 2014") (attached as Exhibit 9); see also Montenigro et al., Clinical Subtypes of Chronic Traumatic Encephalopathy, 6 Alzheimer's Research & Therapy 68, at 1/17 (2014) (noting that CTE "is a neurodegenerative disease" that is "unique" from other diseases, including Alzheimer's) (attached as Exhibit 10); McKee et al. 2013, supra, at 44 (noting that CTE can be "clinically mistaken for Alzheimer's disease or frontotemporal dementia").

¹³ Gavett et al., Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma, 30 Clinical Sports Medicine 179, 184 (2011) (attached as Exhibit 11).

¹⁴ *Id.*; see also Stern et al., Clinical Presentation of Chronic Traumatic Encephalopathy, 81 Neurology 1122, 1124-25 (2013) ("Stern et al. 2013") (attached as Exhibit 12); State of Play: Brain Injuries and Diseases of Aging: Hearing Before the S. Special Comm. on Aging, 113th Cong. 3 (2014), at 5 (written statement of Dr. Robert Stern) ("Stern Testimony"), http://www.aging.senate.gov/imo/media/doc/Stern_6_25_14.pdf; Jordan, *supra*, at 226 box 3 (attached as Exhibit 13).

¹⁵ McKee *et al.* 2013, *supra*, at 51-59.

¹⁶ *Id.* at 52.

symptoms are similar, but also may include suicidality and language difficulties.¹⁷ Stage III involves further cognitive impairment.¹⁸ Stage IV – where "[m]ean brain weight [i]s significantly smaller than lower stage CTE" – involves symptoms including severe memory loss with dementia, profound loss of attention and concentration, language difficulties, aggression, paranoia, and gait difficulties.¹⁹ A more fulsome discussion of CTE is included as Appendix B to this Objection.

2. CTE in the NFL

As Co-Lead Class Counsel explained on its website, "CTE is believed to be the most serious and harmful disease that results from NFL and concussions." Ex. 1 (Seeger Weiss website as of Sept. 3, 2014) (emphasis added). Studies to date have confirmed that an alarming number of NFL players will be afflicted with CTE. The nation's largest brain bank focused on traumatic brain injury recently announced that it had found evidence of CTE in 76 of 79 brains of former NFL players it examined. An earlier study by that same research group reported that of 34 deceased NFL retirees whose brains it had tested for CTE, all but one had the disease. Of those 33, nearly half showed signs of Stage III or Stage IV CTE – CTE's two most severe

¹⁷ *Id.* at 55.

¹⁸ *Id.* at 56.

¹⁹ *Id.* at 57, 59.

²⁰ Seeger Weiss quickly removed that language after oral argument in the Third Circuit on September 10, 2014, where the inadequate representation and failure to compensate CTE, as well as this language on their website, was raised.

²¹ Breslow, 76 of 79 Deceased NFL Players Found to Have Brain Disease, PBS Frontline (Sept. 30, 2014), http://www.pbs.org/wgbh/pages/frontline/sports/concussion-watch/76-of-79-deceas ed-nfl-players-found-to-have-brain-disease/ (attached as Exhibit 14).

²² McKee *et al.* 2013, *supra*, at 59.

stages.²³ And almost all of these players – 94% – were symptomatic during their lifetimes.²⁴ The most common symptoms were "short-term memory loss, executive dysfunction and attention and concentration problems."²⁵

In fact, the NFL's own doctors have recognized the link between neurocognitive impairment and MTBI. When in 1999 Mike Webster, Hall of Fame center for the Pittsburgh Steelers, was examined by a neurologist hand-picked by the NFL as part of his disability application, that neurologist told the disability board: "With the history of multiple head injuries that all football players have and the history that the patient has predominately problems with what appears to be frontal lobe function, I think we can be pretty comfortable that this is related to injury." The Retirement Board later agreed that Webster's medical reports "indicate that his disability is the result of head injuries suffered as a football player with the Pittsburgh Steelers and Kansas City Chiefs." Webster later became the first NFL retiree to be diagnosed with CTE when in 2002, Dr. Bennet Omalu, a forensic pathologist, examined Webster's brain and observed CTE's characteristic tau build-up. Dr. Omalu found CTE again in 2005 and 2006 in former players Terry Long and Andre Waters, who both committed suicide. Dr. Omalu found CTE again in 2005 and 2006 in former

 $^{^{23}}$ *Id*

²⁴ *Id*.

 $^{^{25}}$ Id

²⁶ Fainaru-Wada & Fainaru, *League of Denial* 99 (2013).

²⁷ *Id*.

²⁸ *Id.* at 158, 163.

²⁹ Schwarz, *Expert Ties Ex-Player's Suicide to Brain Damage*, N.Y. Times (Jan. 18, 2007), http://www.nytimes.com/2007/01/18/sports/football/18waters.html?pagewanted=all ("Schwarz 2007") (attached as Exhibit 15).

3. The Settlement Compensates Only a Few Prior Cases of CTE to the Exclusion of Current and Future Cases of CTE

a. Arbitrary Limitation of CTE Awards

Notwithstanding the fact that CTE is "the most serious and most harmful disease that results from NFL and concussions," Ex. 1 (Seeger Weiss website), the Settlement leaves all class members with current and future cases of CTE without compensation. That is because the Settlement defines "qualifying diagnosis" to include "a post-mortem diagnosis of CTE" *only* "[f]or Retired NFL Football Players who died prior to the date of the Preliminary Approval and Class Certification Order." Settlement Ex. B-1 ¶ 5; *see also* Settlement ¶¶ 2.1(yyy), 6.3(a). Thus, while CTE found in a retired player who died on the eve of preliminary approval allows a \$4 million payment, that same condition goes uncompensated if the player dies one day later, after preliminary approval. The conditions afflicting Objectors are among the well-documented symptoms of CTE. *See* Appendix B. Former players like Objectors who currently are managing the cumulative effects of MTBI – many of which are consistent with the presentation of CTE – would receive no compensation and would continue bearing their medical costs even if their condition progresses to full-blown CTE.

That arbitrary limitation on CTE compensation is remarkable: All but three of the 79 deceased NFL players whose brains have been examined for CTE have been diagnosed with the condition. *See* p. 24, *supra*. The ubiquity of CTE in retired NFL players dwarfs the prevalence of the other conditions that receive compensation. For example, one study examining NFL retirees who played at least five seasons between 1959 and 1988 recorded seven cases of ALS, seven cases of Alzheimer's, and three cases of Parkinson's in *3,439* retired players. National Institute for Occupational Safety and Health, *Brain and Nervous System Disorders Among NFL Players* (Jan. 2013), http://www.cdc.gov/niosh/pgms/worknotify/pdfs/NFL_Notification_02.pdf

(attached as Exhibit 16). And Class Counsel's own actuary estimates 31 cases of ALS and 24 cases of Parkinson's disease in the 21,000-member class. Dkt. No. 6167 at 20. Notwithstanding the widespread prevalence of CTE among NFL retirees, the Settlement provides *no compensation* to players with CTE who die after preliminary approval of the Settlement – likely a large percentage of the 21,000-member putative class.

The negative effects of denying compensation to class members like the Objectors who are at an increased risk of CTE will multiply over time. As science advances, it is likely that CTE will be reliably detectable before death; within five to ten years, CTE will likely be diagnosed in the living. Stern Decl. ¶ 38. Yet the Settlement provides no flexibility for modifying the list of qualifying diseases to compensate a pre-death diagnosis of CTE. *See* Settlement § 6.6(c) ("In no event will modifications be made to the Monetary Award levels in the Monetary Award Grid, except for inflation adjustment(s).").

Indeed, the Settlement anticipates relevant advances in science and medicine that will allow a more precise diagnosis of diseases related to MTBI – *but only to disallow recovery*. For example, the Settlement precludes compensation of diseases detected "through a blood test, genetic test, imaging technique, or otherwise" that "has not yet resulted in actual cognitive impairment and/or actual neuromuscular impairment." Settlement § 6.6(b). For individuals with a disease like CTE, which frequently presents first with behavioral and mood symptoms – symptoms that can be as debilitating as CTE's neurocognitive symptoms – the Settlement's rejection of diagnostic testing as a basis for compensation can have a profoundly negative effect: It will prevent individuals with a known degenerative brain disease from using settlement money to access medical care or treatment that might forestall or prevent the onset of neurocognitive impairment.

b. The Representative Plaintiffs Did Not Protect the Interests of Class Members Who Suffer from or Who Are at Risk of Suffering from CTE

Class members had a strong need for representatives who would have pressed for settlement "provisions that can keep pace with changing science and medicine, rather than freezing in place the science" known at the time of settlement. *Amchem*, 521 U.S. at 610-11 (class representation inadequate where settlement did not account for the interests of class members who may develop disease in the future); *Georgine v. Amchem Prods., Inc.*, 83 F.3d 610, 630-31 (3d Cir. 1996) (class representation inadequate because of conflict between currently injured plaintiffs' interest in maximizing current payouts and future plaintiffs' interest in delaying opt-out due to "changing science and medicine" and "difficulty in forecasting what their futures hold"), *aff'd sub nom. Amchem Prods., Inc. v. Windsor*, 521 U.S. 591 (1997). The Representative Plaintiffs did not fulfill this crucial role.

The Representative Plaintiffs *could not* fulfill that role. Neither Representative Plaintiff shares Objectors' interest in securing compensation for *all cases* of CTE. Mr. Turner, who suffers from ALS, has a diagnosed medical condition that receives compensation under the Settlement (and rightly so). Compl. ¶ 7. But he was not poised to represent the interests of those who have suffered different injuries and receive nothing under the Settlement. Mr. Wooden likewise could not represent the interests of the entire class. Objectors currently exhibit MTBI-related injuries that are clinical indications of CTE. Mr. Wooden, by contrast, has not alleged that he suffers from CTE. Nor has he alleged that he is at "[an] increased risk of developing" CTE, even though he does assert such a risk for dementia, Alzheimer's Disease, Parkinson's Disease, and ALS. Compl. ¶ 4. Mr. Wooden's interests therefore lie in securing future compensation for those four afflictions, not in securing payment for the Objectors' conditions and for future cases of CTE. As a result, the proposed subclasses do not "align[][the]

interests and incentives [of] the representative plaintiffs and the rest of the class." *Dewey*, 681 F.3d at 183 (denying class certification where interests of representative plaintiffs and absent class members diverged).

c. There Is No Justification for the Settlement's Failure To Compensate Current and Future Cases of CTE

Class Counsel and the NFL have offered no justification for the Settlement's failure to compensate current and future cases of CTE – while at the same time requiring a release of all CTE claims. Class Counsel have stated that, "[f]or those retired players who have already died, and who did not carry a diagnosis of a compensable disease or condition while living, a postmortem autopsy diagnosis of CTE serves as sufficient evidence of harm for purposes of establishing compensation." Plaintiffs-Respondents' Answer to Rule 23(f) Petition, *In re Nat'l Football League Players' Concussion Injury Litig.*, No. 14-8103, at 14 (3d Cir. July 29, 2014) ("Class Counsel 23(f) Opp."). But there is no reason why a CTE diagnosis *before* preliminary approval should be sufficient to demonstrate entitlement to a multi-million dollar award while a *future* diagnosis entitles a class member to nothing.

Class Counsel and the NFL have also contended that the Settlement need not compensate CTE specifically because it otherwise compensates "actual" or "demonstrated" neurocognitive or neuromuscular "impairment" or "deficits" through the monetary awards for dementia, ALS, Parkinson's, and Alzheimer's. Class Counsel 23(f) Opp. at 14 & 15 n.6; NFL Answer in Opposition to Rule 23(f) Petition, *In re Nat'l Football League Players' Concussion Injury Litig.*, No. 14-8103, at 18 (3d Cir. July 31, 2014) ("NFL 23(f) Opp."). That justification, too, falls short.

CTE's symptoms extend far beyond cognitive impairment – they include "behavioral and mood disorders" that are "just as important, just as serious, and just as amenable to detection and

diagnosis, as cognitive disorders." Stern Decl. ¶ 32; see Appendix B. These behavioral and mood symptoms, moreover, do not always present alongside CTE's cognitive symptoms. In one study, "22 of 33 deceased former athletes with neuropathologically confirmed CTE (and no other abnormal brain findings) were reported to have behavior or mood problems as their initial difficulties, prior to any cognitive impairment," and "[o]nly 10 of 33 were ever diagnosed with dementia at any time prior to death." Stern Decl. ¶ 32; see also Stern et al. 2013, supra, at 1123. In another study of 51 confirmed cases of CTE, only 22 cases progressed to dementia before death. McKee et al. 2013, supra, at 56 tbl. 4. But the Settlement offers nothing for behavioral and mood disorders.

Additionally, dementia typically does not present unless the individual progresses to Stage III or Stage IV CTE. McKee *et al.* 2013, *supra*, at 56 tbl. 4; Stern *et al.* 2013, *supra*, at 1123. Thus, while behavioral and mood symptoms typically present early in CTE's course, *see* Appendix B, the cognitive symptoms that receive compensation under the Settlement do not appear until the disease has progressed to its later stages, depriving class members of the ability to use compensation under the Settlement to seek intervention and medical treatment in the earlier stages of CTE.

Class Counsel's reliance on the Settlement's compensation for dementia to justify the exclusion of CTE is misplaced for yet another reason – it is inconsistent with the Settlement's treatment of Alzheimer's. Like CTE, Alzheimer's is a "neurodegenerative disease[] that can lead to dementia." Stern Decl. ¶ 40. Thus, if monetary awards for dementia suffice to adequately compensate CTE, they should also suffice to compensate Alzheimer's. But CTE and

Alzheimer's are treated differently. Future cases of Alzheimer's are compensated, future cases of CTE are not.³⁰

Nor can Class Counsel and the NFL justify the exclusion of CTE by urging that CTE sufferers might also be afflicted with (and compensated for) ALS, Parkinson's or Alzheimer's. CTE "is a unique disease, easily distinguished from [Alzheimer's Disease] and other diseases." Stern Testimony, supra, at 2; see also Baugh et al., Chronic Traumatic Encephalopathy: Neurodegeneration Following Repetitive Concussive and Subconcussive Brain Trauma, 6 Brain Imaging & Behavior 244, 246 (2012) ("Baugh et al. 2012") (attached as Exhibit 17) (noting "the early presentation and course of CTE can distinguish it from most other causes of dementia"). Thus, it is "pathologically distinct from other neurodegenerative diseases, including Alzheimer's disease and Frontotemporal Lobar Degeneration." Baugh et al. 2012, supra, at 245. And it is "the only known neurodegenerative dementia with a specific identifiable cause; in this case, head trauma." Gavett, supra, at 184 (emphasis added).

The Complaint itself places CTE front-and-center, pleading it as an independent, MTBI-related disease. It alleges that "the NFL has known for decades that MTBI can and does lead to long-term brain injury, including, but not limited to memory loss, dementia, Alzheimer's Disease, Parkinson's Disease, ALS, depression, *and CTE and its related symptoms*." Compl. ¶ 127 (emphasis added). In pleading the NFL's knowledge of the dangers and risks associated with repetitive MTBI, no fewer than *nine paragraphs* specifically reference CTE, encephalopathy, dementia pugilistica, or punch drunk syndrome. *See* Compl. ¶¶ 89, 92, 94, 96,

The Settlement's treatment of Alzheimer's also disposes of Class Counsel's argument that future cases of CTE are uncompensated because CTE cannot be diagnosed while living. Class Counsel 23(f) Opp. at 14. Alzheimer's can currently be diagnosed definitively only through a pathological post-mortem examination of brain tissue. Stern Decl. ¶ 37. Besides, the technology to reliably diagnose CTE (and Alzheimer's) before death is years – not decades – away. *Id.* ¶ 38.

97, 100, 104, 113, 116. By contrast, one paragraph mentions Alzheimer's, *id.* ¶ 118, and one paragraph mentions ALS and Parkinson's, *id.* ¶ 127, when addressing the NFL's knowledge of the dangers. CTE is also central to the Complaint's fraudulent concealment allegations, which plead that the NFL's MTBI Committee publicly attacked researchers who suggested a link between the NFL and CTE. *See, e.g., id.* ¶¶ 170-174, 193-194, 196-197.

The correlation between CTE and the other qualifying diagnoses, moreover, is weak. In one study of 68 individuals with CTE, eight presented with motor neuron disease (such as ALS), seven presented with Alzheimer's Diseases, and six presented with Parkinson's Disease. McKee et al. 2013, supra, at 44, 50-51, 61. Over two-thirds, however, presented only with CTE. Id. And to the extent that ALS (or another motor neuron disorder), Parkinson's, or Alzheimer's presents alongside CTE, CTE itself could have caused the ALS-like, Parkinson's-like, or Alzheimer's-like symptoms; in those situations, the patient is actually suffering from CTE, not ALS, Parkinson's, or Alzheimer's. As one group of scientists wrote, "it is now known that neurologic conditions previously attributed to [Alzheimer's Disease, Parkinson's Disease], and ALS may actually have been related to CTE." Other research also indicates that individuals previously thought to have Alzheimer's disease in reality suffer from CTE.

As CTE becomes more readily detectable before death, the NFL will be able to use this research to further limit payouts to the class. With the ability to diagnose CTE in the living,

³¹ Lehman et al., Neurodegenerative Causes of Death Among Retired National Football League Players, 79 Neurology 1970, 1971 (2012) (attached as Exhibit 18).

³² See Mitsis, supra, at 7 (reporting on test results of former NFL player who "had many features of [Alzheimer's]" and concluding the player suffered from CTE instead); Borden, Brain Trauma Extends Reach into Soccer, N.Y. Times (Sept. 23, 2014) (noting soccer star Bellini, previously thought to have had Alzheimer's, actually suffered from CTE), http://www.nytimes.com/2014/09/24/sports/soccer/soccer-star-bellini-is-found-to-have-had-brain-trauma.html?_r=1 (attached as Exhibit 19).

cases previously diagnosed as ALS, Parkinson's, and Alzheimer's – and compensated as such under the Settlement – could instead be diagnosed as CTE. Class members in that situation will get nothing.

Thus, the Settlement fails to compensate class members suffering what is likely the most common injury attributable to Defendants' conduct.

B. The 75% Offsets Demonstrate Lack of Adequate Representation

The Settlement also imposes offsets that create an additional class conflict. The Settlement *reduces a claimant's award by 75%* for a *single instance* of non-football-related traumatic brain injury ("TBI") or stroke. Settlement §6.7(b)(ii)-(iii). That 75% offset applies regardless of the severity of traumatic brain injury that the player sustained while playing football. And it presumes that a single non-football-related instance of TBI accounts for 75% of a player's MTBI-related injuries, even though that player may have sustained numerous diagnosed and undiagnosed head traumas throughout his NFL career.³³ As Class Counsel have conceded, "[t]housands of football players, many of whom are thought to have suffered more than one hundred mild traumatic brain injuries, are dealing with horrible and debilitating symptoms."³⁴ The 75% offset is both devoid of scientific justification and grossly unfair.

Instances of stroke, moreover, should be compensated injuries, not offsets that reduce recovery, because the NFL itself has increased the risk of stroke for Objectors and other class members. See Amended Complaint, Finn v. Nat'l Football League, No. 2:11-cv-07067-JLL-

³³ The possibility that a class member will sustain a non-football related TBI is not remote. For example, the car insurance industry estimates that the average driver will be involved in a car collision once every 18 years. Des Toups, *How Many Times Will You Crash Your Car?*, Forbes (July 27, 2011 6:50 PM), http://www.forbes.com/sites/moneybuilder/2011/07/27/how-many-times-will-you-crash-your-car/ (attached as Exhibit 20).

³⁴ See Ex. 1.

MAH, Dkt. No. 4 ¶¶ 135-143 (D.N.J. Dec. 8, 2011) (*Finn* Compl.). Traumatic brain injury can increase the risk of stroke and cause damage to the blood vasculature in the brain.³⁵ Dr. Ira Casson, a former chairman of the NFL's MTBI Committee, has found brain microbleeds that "are likely related to head trauma occurring in football at some level." "Statistical analysis determined an association between total number of dings reported at all levels of football and the presence of microbleeds," which added "further support to the suggestion that head trauma is related to" microbleeding.³⁷ Such cerebral microbleeds, moreover, increase the risk of intracerebral hemorrhage and ischemic stroke.³⁸

NFL-administered Toradol injections have magnified this problem. Toradol, a blood-thinning pain-killer, was routinely given to NFL players without their informed consent regarding the health risks of the drug. As a blood-thinning pain-killer, Toradol masks injuries that players may have suffered, encouraging their continued participation in the game and increasing the risk that a player would suffer multiple instances of MTBI in one game. Such repeated exposure to MTBI increased a player's risk of stroke beyond that which would result if the player had not taken Toradol (because more MTBI increases microbleeding, which in turn increases the likelihood of stroke). Thus, the NFL's own negligent and fraudulent actions have

³⁵ See Burke et al., Traumatic Brain Injury May Be an Independent Risk Factor for Stroke, 81 Neurology 1 (2013) (attached as Exhibit 21); Bigler, Neuropsychology and Clinical Neuroscience of Persistent Post-Concussive Syndrome, 14 J. Int'l Neuropsychological Soc'y 1, 8 (2008) ("Thus, in TBI the same mechanisms that stretch the neuron can stretch the blood vessel and this may impair the neurogenic response of the blood vessel.") (attached as Exhibit 22).

³⁶ Casson et al., Is There Chronic Brain Damage in Retired NFL Players? Neuroradiology, Neuropsychology, and Neurology Examinations of 45 Retired Players, 6 Sports Health 384, 391 (2014) (attached as Exhibit 23).

³⁷ *Id*.

³⁸ See Kakar et al., Cerebral Microbleeds: A New Dilemma in Stroke Medicine, 1 J. Royal Soc'y of Med. Cardiovascular Disease 1, 5-7 (2012) (attached as Exhibit 24).

contributed to the prevalence of stroke among retired players. Co-Lead Class Counsel knew of these allegations – indeed, he represents a group of plaintiffs who sued the NFL based in part on its administration of Toradol. *See Finn* Compl. ¶¶ 135-143. But the Settlement makes no mention of these injuries except to release any claims for them and to inexplicably select them as bases for reducing the retired player's compensation.

Representative Plaintiffs did not adequately represent Objectors' interests in eliminating or reducing the offset related to stroke and post-NFL TBI. *Neither Mr. Turner nor Mr. Wooden claims an increased risk of stroke or non-football-related TBI*. As a result, neither can adequately represent those class members who someday may suffer such a stroke or non-football related instance of TBI – and the resulting drop in compensation under the Settlement – due to the NFL's own conduct.

C. The Failure To Credit Seasons Played in NFL Europe Demonstrates Lack of Adequate Representation

The Settlement, while releasing all claims of NFL Europe players, does not award class members "Eligible Season" credit for time spent playing in NFL Europe or its predecessors. Settlement § 6.7(c)(i). Thus, a class member who played five years in the NFL will receive a larger settlement award than a class member who played two years of his career in NFL Europe and three years in the NFL. In effect, veterans of NFL Europe receive no compensation for the time they spent playing there. That is true even though players in NFL Europe undoubtedly sustained repeated concussive and subconcussive impacts, just like players in the NFL. *See* Morey Decl. ¶¶ 4, 6.

Players in NFL Europe experienced repeated MTBI, just like their counterparts in the United States. NFL Europe played on the same size field, for the same length of time, and adopted rules that were rooted in the NFL Rulebook. Morey Decl. ¶ 6. The NFL Europe season,

moreover, lasted ten games, *id.* ¶ 5, which exceeds the "three or more" NFL games required to accrue an eligible season, Settlement § 2.1(kk). And because the NFL Europe season did not overlap with the NFL season, at least some players would play *full seasons* in *both leagues*. Mr. Morey, for example, played 33 games in the 2003 season – ten in NFL Europe and 23 (including pre- and post-season) in the NFL. Morey Decl. ¶ 7.

Nor were the injuries that players sustained in NFL Europe insignificant. Severely injured players were sometimes flown to Birmingham, Alabama for treatment.³⁹ In one season, as many as 70 players in the six-team league were transported back to the United States.⁴⁰

Class Counsel and the NFL offer no justification for the arbitrary discrimination against class members who played in NFL Europe. Indeed, Co-Lead Class Counsel has admitted that the claims of NFL Europe players were bargained away:

This was a complicated transaction. The case was specifically brought to provide help to players in the NFL. NFL Europe, um, is part of the deal, but, you know, nobody, I think, is going to argue that they're playing at the level that the NFL in the United States is playing at or that they're getting hit like they are there. So I'm not saying they should be squeezed out. I'm not poo-pooing that play over there. But I'm simply saying that in the context of a compromise where there's give and take, you know, we had to focus on what our primary objective was, and that was getting help to players playing in the NFL who need it right now.

Audio file: Interview of Chris Seeger, CBS Sports Radio, The Mojo Show, at 9:09-9:45 (aired July 10, 2014) (emphasis added). To sum up Mr. Seeger's comments: The claims of players in

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³⁹ Nicholson, *NFL Europe's Injured Flown to Birmingham*, Birmingham Business Journal (July 1, 2001), http://www.bizjournals.com/birmingham/stories/2001/07/02/story2.html?page=all (attached as Exhibit 25); *see also* Battista, *A Player's Concussion, a Family's Ordeal*, The N.Y. Times (Sept. 15, 2012) (describing the career-ending hit one NFL Europe player suffered during training camp), http://www.nytimes.com/2012/09/16/sports/football/former-nfl-player-mitch-white-learns-to-adjust-to-postconcussion-life.html?pagewanted=all (attached as Exhibit 26).

⁴⁰ Nicholson, *supra*.

NFL Europe were bargained away to serve the "primary objective" of "getting help to players playing in the NFL."

Neither Mr. Turner nor Mr. Wooden alleges that he played in NFL Europe. Thus, neither adequately represents the interests of players who did, explaining why NFL Europe players are treated disparately. *See GM Trucks*, 55 F.3d at 800 (finding class representation inadequate where "settlement appears to create antagonism within the class").⁴¹

* * * * *

Simply put, distinct groups within the class had their rights bargained away without adequate representation. These intra-class conflicts preclude certification of the settlement class. "The class representatives may well have thought that the Settlement serves the aggregate interests of the entire class." *Amchem*, 521 U.S. at 627. However, where "the interests of the representative plaintiffs and the interests of [absentee class members] align[] in opposing directions," class representation is inadequate. *Dewey*, 681 F.3d at 188; *see also Amchem*, 521 U.S. at 627 (denying class certification where settlement not agreed to by representatives of all sub-classes); *Ortiz v. Fibreboard Corp.*, 527 U.S. 815, 856 (1999) (holding that intra-class conflict "require[d] division into homogenous subclasses ... with separate representation to eliminate conflicting interests"). 42

⁴¹ Players in NFL Europe are not the only NFL veterans who go without full credit for the time they spent in the league. Class members who spent time on "practice, developmental, or taxi squad roster[s] for at least eight (8) regular or postseason games" receive only "half of an Eligible Season." Settlement ¶ 2.1(kk).

⁴² If the Court agrees that intra-class conflicts prevent certification, it may "simply divide the groups into subclasses," *Dewey*, 681 F.3d at 189, so that "separate counsel [can] provide[] adequate structural protections to assure that differently situated plaintiffs negotiate for their own unique interests," *In re Warfarin Sodium Antitrust Litig.*, 391 F.3d 516, 533 (3d Cir. 2004) (quotation marks omitted).

II. The Notice Is False, Misleading, and Inconsistent with Rule 23 and Due Process

Through misleading language, confusing juxtaposition, and outright false statements, the notice obscures the fact that the Settlement bargains away the rights of a large portion of the class in a way that will provide those class members with no compensation. Courts in class actions and other areas of law have construed such defects to be legally inadequate. Class Counsel have compounded the problem of inadequate notice by engaging in a propaganda campaign advocating the Settlement.

Approval of a class settlement under Rule 23(b)(3) requires that class counsel furnish notice in compliance with Rules 23(c)(2) and (e). *See Manual for Complex Litigation* (4th) §21.311-.312. Rule 23(c)(2) requires "the court [to] direct to class members the best notice that is practicable under the circumstances" that "clearly and concisely state[s] in plain, easily understood language" the nature of the action, the claims and defenses asserted, and the right of class members to request exclusion. Fed. R. Civ. P. 23(c)(2)(B). Rule 23(e) requires the court to approve any settlement, and to "direct notice in a reasonable manner to all class members who would be bound by the proposal." Fed. R. Civ. P. 23(e)(1).

Notice protects class members' due process rights. *See, e.g., Larson v. AT&T Mobility LLC*, 687 F.3d 109, 126 (3d Cir. 2012) (notice scheme deficient when it did not require defendant to search billing records to identify affected class members, and vacating approval of settlement). In *Larson*, for example, the Third Circuit explained that it is "stringent in enforcing the individual notice requirement" because "a procedure such as the class action, which has a formidable if not irretrievable, effect on substantive rights, can comport with constitutional standards of due process only if there is a maximum opportunity for notice to the absentee class member." *Id.* at 126 (quotation marks omitted).

Notice is insufficient when it is false or misleads class members about the terms of the settlement. *See Eubank v. Pella Corp.*, 753 F.3d 718, 728 (7th Cir. 2014) (vacating approval of settlement, in part because notice was "incomplete and misleading" and did not "provide a truthful basis for deciding whether to opt out."); *In re Katrina Canal Breaches Litig.*, 628 F.3d 185, 197-98 (5th Cir. 2010) (vacating approval of settlement where notice "did not inform class members of the possibility that they would not receive any direct benefit from the settlement" and "did not provide interested parties with knowledge critical to an informed decision as to whether to object to class certification and settlement."); *Molski v. Gleich*, 318 F.3d 937, 951 (9th Cir. 2003) (vacating approval of settlement, in part because "notice misled the putative class members" about which kinds of claims would be released).

A. The Notice Contains Overtly False and Misleading Statements

The notice misleads class members about the basic compromise of the settlement because it fails to alert class members to the fact that they will not be compensated for current or future CTE, while significantly limiting the NFL Defendants' liability.

1. The Short Form Notice

The short form notice, which was extensively publicized, is patently false. Dkt. No. 6093-2 ("Short Form Notice"). It was required to appear as a full-page, color advertisement in *Ebony, People, Sports Illustrated*, and *Time* magazines, and was downloadable on the settlement website, at www.nflconcussionsettlement.com ("Settlement Website"). Dkt. No. 6073-3 (Kinsella Decl.) at 6-7. According to the notice plan, the Short Form Notice "is designed to get the reader's attention" and "concisely and clearly states, in plain easily understandable language, all required information." *Id.* at 10.

The first sentence of the Short Form Notice assures players that their "valid claims" will be "paid in full" for 65 years:

NFL Concussion Settlement

All Valid Claims of Retired NFL Football Players to be Paid in Full for 65 Years Monetary Awards, Baseline Medical Exams and Other Benefits Provided

The Short Form Notice continues, with more detail about the benefits of the Settlement:

The Settlement provides money for three benefits:

- Baseline medical exams to determine if retired players suffer from neurocognitive impairment and are entitled to additional testing and/ or treatment (\$75 million),
- Monetary awards for diagnoses of ALS (Lou Gehrig's disease), Alzheimer's Disease, Parkinson's Disease, Dementia and certain cases of chronic traumatic encephalopathy or CTE (a neuropathological finding) diagnosed after death. The maximum monetary awards range from \$1.5 million to \$5 million depending on the diagnosis. All valid claims will be paid in full for 65 years; and
- Education programs and initiatives related to football safety (\$10 million).

This language plainly states that "[t]he Settlement will provide . . . [m]onetary awards for . . . certain cases of chronic traumatic encephalopathy (CTE) (a neuropathological finding) diagnosed after death," and proclaims that "all valid claims will be paid in full for 65 years." Dkt. No. 6093-2. A player reading this language – who might be concerned about CTE – would reasonably, but incorrectly, conclude that even though he might not get compensated for developing CTE during his lifetime, at least after his death his family will be compensated.

Nearly identical language appears on the front page of the Settlement Website:

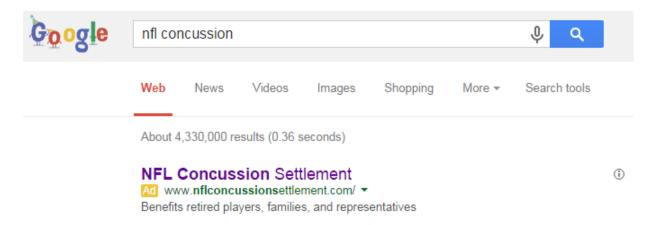
Retired players, legal representatives of incapacitated or deceased players, and families of deceased players may be eligible to receive benefits from this Settlement.

The proposed settlement provides for three benefits:

- 1. Baseline medical exams for retired NFL players;
- Monetary awards for diagnoses of ALS (Lou Gehrig's disease), Alzheimer's
 Disease, Parkinson's Disease, Dementia and certain cases of chronic traumatic
 encephalopathy or CTE (a neuropathological finding) diagnosed after death; and
- 3. Education programs and initiatives related to football safety.

All valid claims for injury will be paid in full for 65 years.

NFL Concussion Settlement, http://www.nflconcussionsettlement.com (last visited Oct. 3, 2014). The website was advertised using paid links on popular search engines like Google. Kinsella Decl. at 10. Thus, any player curious about the Settlement who types the phrase "NFL concussion" into Google is greeted with a paid link to the Settlement Website as the first result:



Once he has clicked, the Settlement Website provides the misleading language, described above, about benefits for players who die with a diagnosis of CTE.

2. The Long Form Notice

The long form notice was direct-mailed to readily identifiable retired players, and was available for download on the Settlement Website. Dkt. No. 6093-1 ("Long Form Notice"), available at https://www.nflconcussionsettlement.com/Documents/Long-form Notice.pdf; Kin-

sella Decl. at 9. A full-color, glossy booklet invoking football imagery, the Long Form Notice does more to mislead than to educate class members.

While the Long Form notice does reveal the cut-off for CTE claims, it does so obliquely. It states:

5. WHAT ARE THE BENEFITS OF THE SETTLEMENT?

Under the Settlement, the NFL Parties will pay to fund:

- Baseline neuropsychological and neurological examinations for eligible retired players, and additional
 medical testing, counseling and/or treatment if they are diagnosed with moderate cognitive impairment
 during the baseline examinations (up to \$75 million, "Baseline Assessment Program") (see Questions
 11-13);
- Monetary awards for diagnoses of Death with CTE prior to July 7, 2014, ALS, Parkinson's Disease,
 Alzheimer's Disease, Level 2 Neurocognitive Impairment (i.e., moderate Dementia) and Level 1.5
 Neurocognitive Impairment (i.e., early Dementia) (see Questions 14-21). All valid claims under the
 Settlement, without limitation, will be paid in full throughout the 65-year life of the Settlement (the
 "Monetary Award Fund"); and

Long Form Notice at 7. This language does not outright disclose that players who die with a diagnosis of CTE after July 7, 2014, will not be compensated. Instead, it states that "the NFL Parties will pay to fund . . . [m]onetary awards for diagnoses of Death with CTE prior to July 7, 2014" and leaves it to the reader to conclude that every other class member with CTE will not be compensated for that disease.

In any event, this flash of "candor" is overwhelmed by repeated false and misleading statements about CTE. In the "Monetary Awards" section, on which players might reasonably focus, the Long Form Notice states:

14. WHAT DIAGNOSES QUALIFY FOR MONETARY AWARDS?

Monetary awards are available for the diagnosis of ALS, Parkinson's Disease, Alzheimer's Disease, Level 2 Neurocognitive Impairment (i.e., moderate Dementia), Level 1.5 Neurocognitive Impairment (i.e., early Dementia) or Death with CTE (the "Qualifying Diagnoses"). A Qualifying Diagnosis may occur at any time until the end of the 65-year term of the Monetary Award Fund.

Long Form Notice at 12. The notice states that "Death with CTE" is a "Qualifying Diagnosis." The term "Qualifying Diagnosis" is likewise defined in the notice to include "Death with CTE."

But many statements in the notice are false when applied to "Death with CTE." For example, the notice states that "[a] Qualifying Diagnosis may occur at any time until the end of the 65-year term of the Monetary Award Fund," which is false as applied to *every* future diagnosis of "Death with CTE." Similarly, in the same section on monetary benefits:

21. CAN I RECEIVE A MONETARY AWARD EVEN THOUGH THE RETIRED PLAYER IS DEAD?

Yes. Representative Claimants for deceased retired players with a Qualifying Diagnoses will be eligible to receive monetary awards. If the deceased retired player died before January 1, 2006, however, the Representative Claimant will only receive a monetary award if the Court determines that a wrongful death or survival claim is allowed under applicable state law.

Derivative Claimants also will be eligible for a total award of 1% of the monetary award that the Representative Claimant for the deceased retired player receives (see Question 16).

Representative and Derivative Claimants will also need to register for Settlement benefits (see Question 26).

Long Form Notice at 16. Contrary to this assertion in the notice, Representative Claimants for deceased retired players who die with a diagnosis of CTE are, as a category, *not* eligible to receive monetary awards. A player with CTE is eligible only if he died by July 7, 2014. The notice compounds the deception by stating that "[i]f the deceased retired player died before January 1, 2006, however, the Representative Claimant will only receive a monetary award if the Court determines that a wrongful death or survival claim is allowed under applicable state law." *Id.* This language creates the misimpression that while there may be limits on compensation for those who die before January 1, 2006, those who die after will be compensated. That is not true.

The "Monetary Awards" section also includes a table showing award amounts:

QUALIFYING DIAGNOSIS	MAXIMUM AWARD AVAILABLE
Amyotrophic lateral sclerosis (ALS)	\$5 million
Death with CTE (diagnosed after death)	\$4 million
Parkinson's Disease	\$3.5 million
Alzheimer's Disease	\$3.5 million
Level 2 Neurocognitive Impairment (i.e., moderate Dementia)	\$3 million
Level 1.5 Neurocognitive Impairment (i.e., early Dementia)	\$1.5 million

Long Form Notice at 13. The table lists "Death with CTE" as a "Qualifying Diagnosis" in a column along with ALS, Parkinson's, Alzheimer's, Level 2 Neurocognitive Impairment, and Level 1.5 Neurocognitive Impairment. The maximum award for "Death with CTE" is listed as \$4 million. Nowhere in this section does it state that players will be compensated for "Death with CTE" only if they die before July 7, 2014. Instead, the notice suggests to readers that "Death with CTE" will be treated similarly to the other diseases, which have no cut-off date. The next table is equally misleading:

AGE AT DIAGNOSIS	ALS	DEATH w/CTE	PARKINSON'S	ALZHEIMER'S	LEVEL 2	LEVEL 1.5
Under 45	\$5,000,000	\$4,000,000	\$3,500,000	\$3,500,000	\$3,000,000	\$1,500,000
45 - 49	\$4,500,000	\$3,200,000	\$2,470,000	\$2,300,000	\$1,900,000	\$950,000
50 - 54	\$4,000,000	\$2,300,000	\$1,900,000	\$1,600,000	\$1,200,000	\$600,000
55 - 59	\$3,500,000	\$1,400,000	\$1,300,000	\$1,150,000	\$950,000	\$475,000
60 - 64	\$3,000,000	\$1,200,000	\$1,000,000	\$950,000	\$580,000	\$290,000
65 - 69	\$2,500,000	\$980,000	\$760,000	\$620,000	\$380,000	\$190,000
70 - 74	\$1,750,000	\$600,000	\$475,000	\$380,000	\$210,000	\$105,000
75 - 79	\$1,000,000	\$160,000	\$145,000	\$130,000	\$80,000	\$40,000
80+	\$300,000	\$50,000	\$50,000	\$50,000	\$50,000	\$25,000

Id. at 14. The table shows how awards decrease with age at diagnosis. It creates the misleading impression that, as with the other listed diseases, claims for "Death w/CTE" will be paid out to players who are diagnosed potentially many years in the future when they are older. Any player reading this section on monetary compensation would be left with the clear, but false, understanding that he will be compensated if he dies with CTE, just as he would if he developed ALS or one of the other diseases listed as a "Qualifying Diagnosis." But any player who lives to read the notice will not be eligible for compensation for CTE under the Settlement.

These tables are misleading in other ways. Notwithstanding the presence of multimillion dollar payments, the notice does not disclose that Class Counsel's own actuary predicts that many class members will never realize these maximum awards. For example, Class Counsel's actuary estimates the average claimant will be 77 years old at the time of diagnosis, Dkt. No. 6167 at 7, which will reduce the ALS award by 80% and reduce the awards for CTE, Parkinson's, Alzheimer's, and Level 2 dementia by 96% to 97%, Settlement Ex. 3. Nor does the notice disclose that Class Counsel's actuary predicts only 3,600 class members – out of 21,000 – are estimated to receive any monetary compensation at all. Dkt. No. 6167 at 3-4.

The notice has the same shortcomings as notices courts have found inadequate in other settlement cases. Like the notice in *Eubank*, 753 F.3d at 728, which the court found deficient because it implied that class members would receive cash even though some would only be entitled to coupons, the notice implies that those who die with a diagnosis of CTE will be compensated up to \$4 million – even though only those who die by July 7, 2014 will be compensated. *See also Katrina Canal Breaches Litig.*, 628 F.3d at 197-98 (settlement vacated when notice failed to inform class members that they might not receive any direct benefit from the settlement). Like the notice in *Molski*, 318 F.3d at 951, which the court found misleading

because it implied that the settlement would preserve certain claims, the NFL players' notice misleadingly implies that CTE claims will be compensable over the life of the Settlement. In fact, they will not.

B. The Notice Is Similar to Communications Courts Have Found Misleading in Other Contexts

The NFL Defendants and Class Counsel cling to the few statements of truthful information about the CTE benefit in the notice, and argue that this somehow offsets deception elsewhere. However, the law generally recognizes that the limited disclosure of truthful information amidst a sea of false and inaccurate information cannot salvage a communication from being misleading.

When a communication contains misleading statements, the fact that it may contain some truth will not save it if it still misleads taken as a whole. The Supreme Court has noted that "not every mixture with the true will neutralize the deceptive." *Va. Bankshares, Inc. v. Sandberg*, 501 U.S. 1083, 1097 (1991) (finding that true statements embedded among misleading ones in a proxy statement were insufficient to render the proxy as a whole not misleading); *SEC v. Rana Research, Inc.*, 8 F.3d 1358, 1363 (9th Cir. 1993) (denying defendants' motion for summary judgment in securities fraud action because "grain of truth embedded" in subsequent press release did not neutralize misleading statements in earlier press release); *Marksman Partners, L.P. v. Chantal Pharm. Corp.*, 927 F. Supp. 1297, 1307-08 (C.D. Cal. 1996) (disclosure of truthful information in the appendix of a Form 10-K submission did not as a matter of law dispel the effect of misleading accounting statements).

In analyzing proxy statements and offering materials or prospectuses for securities, courts have determined that a statement "can also be misleading, though not technically false, if it amounts to a half-truth by omitting some material fact." *Fogarazzo v. Lehman Bros., Inc.*, 341

F. Supp. 2d 274, 294 (S.D.N.Y. 2004) (plaintiff sufficiently alleged a misrepresentation in a securities fraud action concerning misleading research reports). Thus, courts have recognized that what matters "is not whether the particular statements, taken separately, were literally true, but whether . . . [the] representations, taken together and in context, would have misled." *In re Lehman Bros. Sec. & ERISA Litig.*, 799 F. Supp. 2d 258, 314 (S.D.N.Y. 2011) (denying motion to dismiss because the court could not conclude as a matter of law that "inconspicuous and scattered warnings" neutralized "repeated and emphasized [misleading] statements" in the offering materials for a security). In determining whether communications are misleading, taken as a whole, courts have looked to "the prominence of disclosures or warnings as a factor." *Johnson v. NYFIX, Inc.*, 399 F. Supp. 2d 105, 121 (D. Conn. 2005) (finding that plaintiff adequately alleged that financial statements were misleading in a securities fraud action).

Courts have analyzed misleading communications in the context of false advertising claims similarly. In an advertisement, "statement[s], although literally true, can for all practical purposes, convey a false message." *Johnson & Johnson-Merck Consumer Pharm. Co. v. Procter & Gamble Co.*, 285 F. Supp. 2d 389, 392-93 (S.D.N.Y. 2003) (advertisement created a misleading impression despite being literally true, and a disclaimer was "insufficient to dispel the false message"); *Castrol Inc. v. Pennzoil Co.*, 987 F.2d 939, 946 (3d Cir. 1993) (noting that "a court must analyze the message conveyed [in an advertisement] in full context" and upholding trial court finding that advertisement claims were literally false by necessary implication). Courts also recognize that evidence of actual confusion among people who are the target of a communication is relevant, and that "[e]ven if an advertisement is not literally false, relief is available . . . if it can be shown that the advertisement has misled, confused, or deceived the consuming public." *Southland Sod Farms v. Stover Seed Co.*, 108 F.3d 1134, 1140 (9th Cir.

1997) (reversing district court's grant of summary judgment in favor of defendant in a false advertising action because triable issues of fact existed as to whether consumers were actually deceived by literally true statements).

Consumer protection laws apply the same analysis. Under Massachusetts consumer protection law, for example, "advertising need not be totally false in order to be deemed deceptive." Aspinall v. Philip Morris Cos., 813 N.E.2d 476, 487 (Mass. 2004) (granting class certification in an action involving advertisements in which cigarette manufacturers implied "light" cigarettes contained less nicotine and tar). "The criticized advertising may consist of a half truth, or even may be true as a literal matter, but still create an over-all misleading impression through failure to disclose material information." Id. Under California's Unfair Competition Law, Cal. Bus. & Prof. Code §§ 17200 et seq., fraudulent business practices include those "based on representations to the public which are untrue, and also those which may be accurate on some level but will nonetheless tend to mislead or deceive." McKell v. Wash. Mut., Inc., 49 Cal. Rptr. 3d 227, 239 (Cal. Ct. App. 2006). Under the Federal Trade Commission Act, 15 U.S.C. §§ 45 and 52, "[t]he failure to disclose material information may [also] cause an advertisement to be deceptive, even if it does not state false facts." Sterling Drug, Inc. v. FTC, 741 F.2d 1146, 1154 (9th Cir. 1984) (finding advertisement was misleading as to whether it contained aspirin as a pain-killer). Moreover, courts recognize that "[a] few words of disclaimer [can be] lost when [a communication is] considered as a whole." McNeil-PPC, Inc. v. Pfizer, Inc., 351 F. Supp. 2d 226, 254 (S.D.N.Y. 2005) (granting a preliminary injunction in a case where an advertisement misleadingly suggested that mouthwash was a replacement for flossing, even though the ads contained a disclaimer telling consumers "[t]here's no replacement for flossing.").

These principles apply with no less force when considering whether the notice here, taken as a whole, is misleading to players and their families. As is the case with proxy statements, where people are asked to vote as to their rights on the basis of complex documents, a "grain of truth embedded" in the Long Form Notice, *Rana Research*, 8 F.3d at 1363, should not save an otherwise misleading notice. That is particularly true when the "disclosure" is not featured prominently in the highly publicized and distributed Short Form Notice, nor in the Long Form Notice's section describing "Monetary Benefits," the section players are most likely to read. Were the situation not so serious, it would be ironic that individuals entitled to compensation due to cognitive injures are being asked to navigate this complex maze to simply learn their rights. "The point of a [notice], after all, should be to inform, not to challenge the [players'] critical wits." *Va. Bankshares*, 501 U.S. at 1097.

C. Class Counsel's Propaganda Campaign Has Compounded the False and Misleading Nature of the Notice

To make matters worse, Class Counsel – who stand to receive a huge payday upon approval – have falsely described the Settlement to the media. The propaganda campaign started shortly after the preliminary approval of the Settlement. An article in the *New York Times* quoted Co-Lead Class Counsel's representations about the CTE benefit:

[O]ne of the lead lawyers for the plaintiffs in the class action, said the objectors had misread the settlement. The families of dead players who were found to have C.T.E. might receive awards because the players could no longer receive a diagnosis. C.T.E. was not included for living players because the settlement would cover those symptoms if they were to develop.

'Going forward, any retired player who is sick with a qualifying condition will get compensated, as C.T.E. cannot be currently diagnosed in living people,' he said. 'Whether you have C.T.E. or not, or whether or not you can prove you have

C.T.E., if you have symptoms of a qualifying condition, you will be compensated. '43

A recent article in Sporting News further stated: "[t]he attorneys representing the players in the NFL concussion lawsuit are now at work getting the word out to all the retired players affected by the revised settlement." Co-Lead Class Counsel states in the article that "CTE is not a relevant marker for anything in this settlement. It's the symptoms – if you have all the symptoms that are related to CTE, or the diseases that are related, like dementia and Alzheimer's and ALS, then that determines it. If a player thinks he has any symptoms of it, that's the very reason to stay in the deal." *Id.* But Co-Lead Class Counsel's hypothetical player, someone who "thinks he has any symptoms of [CTE]" and "stay[s] in the deal" will only get compensated if he is diagnosed with one of the other qualified diseases. That hypothetical player may well get no compensation at all in return for "stay[ing] in the deal" and bargaining away his right to sue the NFL Defendants for his injuries. But that hypothetical player, reading the notice in light of Co-Lead Class Counsel's public comments, is likely to be misled into thinking otherwise.

An article that appeared on *profootballconcussions.com*, which bills itself as "A Fan's Look at Head Injuries and the Concussion Crisis," repeated Co-Lead Class Counsel's misleading

⁴³ Belson, *For Retirees, Decision on Concussion Settlement Will Not Be a Simple One*, N.Y. Times (July 22, 2014), http://www.nytimes.com/2014/07/23/sports/football/nfl-concussion-settlement-divides-former-players.html? r=0 (attached as Exhibit 27).

⁴⁴ Steele, *Players Wrong on Key Factor in NFL Concussion Settlement*, Sporting News (July 14, 2014), http://www.sportingnews.com/nfl/story/2014-07-14/nfl-concussions-lawsuit-cte-symptom s-eligible-settlement-tony-dorsett-wycheck-seeger (attached as Exhibit 28).

⁴⁵ See Stern Decl. ¶ 41 ("The only symptoms related to CTE that are compensable (other than those that overlap with Alzheimer's disease, ALS or Parkinson's) are cognitive difficulties, and only cognitive difficulties that are severe enough that the Class Member would have significant impairments in critical aspects of daily living and independence. Several key symptoms of CTE that are identified in the scientific and medical literature and in my clinical and research experience are not compensable.").

assertions: "If you get sick, period, you still get paid. We're telling everybody to go get tested. You'll be in the system. You're protected (by the settlement)."

In an article in ABC News, which discusses former player Junior Seau, who committed suicide in 2012 and was diagnosed after his death with CTE, Co-Lead Class Counsel is quoted as saying:

If Mr. Strauss [the lawyer for Seau's family] believes the \$4 million his client is eligible for under the settlement is insufficient, he can choose to permanently forfeit these benefits and face all the significant risks associated with continued litigation We would advise any class member against opting out of this agreement, considering the tremendous guaranteed benefits it provides.⁴⁷

Co-Lead Class Counsel fails to mention that had Mr. Seau died today, his family would be entitled to nothing.

In an article on *SportsIllustrated.com*,⁴⁸ Co-Lead Class Counsel again hyped the Settlement: "There is no scenario where a player won't get paid . . . [t]he biggest news of this is that in 15 or 25 years, you are still guaranteed to be compensated." Like Co-Lead Class Counsel's other public statements, this one is calculated to mislead players into believing that they are signing onto a comprehensive settlement, when in fact the Settlement fails to cover a significant class of claims.

An article in USA Today, which quoted Co-Lead Class Counsel extensively, states:

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⁴⁶ *The NFL CTE Question*, The Pro Football Concussion Report (July 22, 2014), http://profootballconcussions.com/the-nfl-cte-question (attached as Exhibit 29).

⁴⁷ Fainaru-Wada & Fainaru, *Seaus to Opt Out of Concussion Deal*, ABC News (Sept. 3, 2014), http://abcnews.go.com/Sports/seaus-opt-concussion-deal/story?id=25230257 (attached as Exhibit 30).

⁴⁸ DeGory, *New Concussion Settlement a Win-Win*, SportsIllustrated.com (June 26, 2014), http://mmqb.si.com/2014/06/26/new-concussion-settlement-kevin-turner (attached as Exhibit 31).

"This is the only program where everybody gets justice. . . . Everybody wins," [Co-Lead Class Counsel] said.

He said all retired players, not just those who sued, will be eligible for a brain assessment program, and those found to have a certain level of impairment will receive a medical benefit card that be used for further testing and treatment. . . .

[Co-Lead Class Counsel] said former players will not have to prove their brain conditions are linked to NFL concussions.

"You don't have to prove that your neurological problem is related to a concussion. You don't have to prove in the settlement that you sustained a concussion in the NFL," [Co-Lead Class Counsel] said. "You just need to be a former retired player and you're in the program."

"You just need to be a former retired player and you're in the program." This language is superbly calculated to reassure players of something that is just not true – that the Settlement is comprehensive and will take care of them no matter what happens. Co-Lead Class Counsel makes no mention of the limitation on CTE compensation. Further, in saying "you don't have to prove in the settlement that you sustained a concussion in the NFL," he fails to mention that you do if you wish to avoid the 75% offset for non-NFL TBI. In cheerleading the Settlement, he has been deceiving players about what the Settlement covers.

As the deadline for opting out draws near, the propaganda has intensified. Co-Lead Class Counsel recently gave an interview on *Real Football Lives and Wives*, an online radio program aimed at the families of current and retired NFL players.⁵⁰ Over the course of 45 minutes, Co-Lead Class Counsel extensively discussed the Settlement and exhorted class members to not opt out. However, at no time during the entire interview did Co-Lead Class Counsel ever mention

⁴⁹ Mihoces, *NFL Reaches Concussion Settlement*, USA Today (Aug. 29, 2013), http://www.usatoday.com/story/sports/nfl/2013/08/29/nfl-concussion-settlement-judge-anita-brodytony-dorsett-jim-mcmahon-junior-seau/2727483 (attached as Exhibit 32).

⁵⁰ NFL Concussion Settlement, REAL Information You Need to Know, Real Football Wives (and Lives) (Sept. 2, 2014), http://www.blogtalkradio.com/realfootballwives/2014/09/02/nfl-concuss ion-settlement-real-information-you-need-to-know.

that the families of players who die with a diagnosis of CTE after July 7, 2014, will receive no compensation. Nor did he mention that Class Counsel's own actuary estimates that only 3,600 out of 21,000 class members will receive any monetary compensation at all. Dkt. No. 6167 at 3-4.

"Whether a claimant would want to accept or reject the proposed settlement is a decision to be made by him independently and without influence or pressure from those competing parties who either favor or oppose the settlement." *Phila. Housing Auth. v. Am. Radiator & Standard Sanitary Corp.*, 323 F. Supp. 364, 378 (E.D. Pa. 1970). By combining the misleading notice with a misleading propaganda campaign, Class Counsel have fundamentally undermined the ability of class members to make this decision "without influence or pressure."

D. False and Misleading Notice Has, in Fact, Misinformed Players and Falsely Assured Them That the Settlement Provides Benefits It Lacks

The confusion caused by the notice is not theoretical, it is real. In an article on *Sports On Earth*, columnist Patrick Hruby describes his conversation with former player Dave Pear:

"Is it a good deal?" Pear said. "It only covers certain people at certain times. Based on what I've read, you won't get compensation for CTE [chronic traumatic encephalopathy] until after you're dead."

Not exactly, I told him. To receive cash awards for CTE, a neurodegenerative disease that currently only can be diagnosed posthumously, former players must have died by a specific cutoff date.⁵¹

The media is confused too: In a recent article, 52 ESPN characterized the settlement:

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⁵¹ Hruby, *Cutting them Short*, Sportsonearth.com (July 18, 2014), http://www.sportsonearth.com/article/85045740/nfl-concussion-settlement-cuts-cte-coverage-short-patrick-hruby (attached as Exhibit 33).

⁵² Fainaru & Fainaru-Wada, *Brain Impairment Begins Younger*, ESPN.com (Sept. 13, 2014), http://espn.go.com/nfl/story/_/id/11513442/data-estimates-3-10-nfl-retirees-face-cognitive-woes (attached as Exhibit 34).

The plan would pay up to \$5 million for players with amyotrophic lateral sclerosis, also known as Lou Gehrig's disease; \$4 million for deaths involving CTE; \$3.5 million for Alzheimer's disease; and \$3 million for moderate dementia and other neurocognitive problems.

However, only men younger than 45 who spent at least five years in the league would get those maximum payouts. The awards are reduced, on a sliding scale, if they played fewer years or were diagnosed at a more advanced age.

This description of the settlement seems to be taken straight from the false and misleading notice. Even though it takes care to note other limitations of the Settlement, such as the sliding scale of awards for players over 45, it fails to mention that CTE claims will only be compensated if the player dies by July 7, 2014, and misleadingly implies that all "deaths involving CTE" are eligible for up to \$4 million. Showing the reach of Class Counsel's propaganda campaign, these two paragraphs appeared in nearly identical form in write-ups published in September 2014 on the websites of the *Wall Street Journal*, ⁵³ the *Philly.com Blog*, ⁵⁴ *Huffington Post*, ⁵⁵ *FoxSports.com*, ⁵⁶ the *Dallas Morning News*, ⁵⁷ and the *Minneapolis Star Tribune*. ⁵⁸ None of these sources noted the July 7, 2014 cut-off date for CTE claims.

⁵³ Dale, *NFL: Nearly Three in 10 Ex-Players Will Develop Debilitating Conditions*, Associated Press (Sept. 12, 2014), *republished at* http://online.wsj.com/articles/nfl-nearly-three-in-10-explayers-will-develop-debilitating-brain-conditions-1410571935 (attached as Exhibit 35).

⁵⁴ Available at http://www.philly.com/philly/blogs/sports/eagles/20140912_ap_0487fc0938bf47 d9836b379dee6f9aca.html (attached as Exhibit 36).

⁵⁵ Available at http://www.huffingtonpost.com/2014/09/12/nfl-players-alzheimers-dementia_n_5812504.html (attached as Exhibit 37).

⁵⁶ Available at http://www.foxsports.com/nfl/story/nfl-players-lawyers-detail-lasting-effects-of-concussions-091214 (attached as Exhibit 38).

⁵⁷ Available at http://www.dallasnews.com/sports/dallas-cowboys/headlines/20140912-players-lawyers-data-estimates-3-in-10-nfl-retirees-face-cognitive-woes.ece (attached as Exhibit 39).

⁵⁸ Available at http://www.startribune.com/lifestyle/health/274914621.html (attached as Exhibit 40).

III. The Settlement Is Unfair, Unreasonable, and Inadequate

A class settlement cannot be approved unless it "is fair, reasonable, and adequate." Fed. R. Civ. P. 23(e). Where, as here, a class settlement is negotiated *before* certification, the Court must "be even more scrupulous than usual in approving" the settlement because "the 'danger of a premature, even a collusive, settlement [is] increased.'" *GM Trucks*, 55 F.3d at 788, 805. Consequently, for pre-certification settlements, the settling parties must "make a higher showing of fairness to sustain the [] settlement []." *Id.* at 805.⁵⁹

In assessing whether a settlement is fair, reasonable, and adequate, the Court must consider: (1) the stage of the proceedings and the amount of discovery; (2) the ability of the NFL to withstand a greater judgment; (3) the reaction of the class; (4) the risks of establishing liability and damages; (5) the reasonableness of the settlement in light of the best possible recovery and the attendant risks of litigation; (6) the likelihood of maintaining class status throughout the litigation; and (7) the complexity, expense, and likely duration of the litigation. *Girsh v. Jepson*, 521 F.2d 153, 157 (3d Cir. 1975); *In re Cendant Corp. Litig.*, 264 F.3d 201, 232 (3d Cir. 2001) (applying the *Girsh* factors). Each of these factors demonstrates why the Settlement should not be approved.

⁵⁹ See also Ace Heatin

⁵⁹ See also Ace Heating & Plumbing Co. v. Crane Co., 453 F.2d 30, 33 (3d Cir. 1971) ("[W]hen the settlement is not negotiated by a court designated class representative the court must be doubly careful in evaluating the fairness of the settlement to the plaintiff's class."); In re Gen. Motors Corp. Engine Interchange Litig., 594 F.2d 1106, 1125 (7th Cir. 1979) (attributing a need for heightened scrutiny of the settlement to the potential for collusive settlement); Weinberger v. Kendrick, 698 F.2d 61, 73 (2d Cir. 1982) (higher showing of fairness required in pre-certification settlements, and special focus on assuring adequate representation and the absence of collusion); Mars Steel, 834 F.2d at 681 (noting "a more careful scrutiny of the fairness of the settlement is required"); Simer v. Rios, 661 F.2d 655, 664-66 (7th Cir. 1981) (requiring a higher showing of fairness where settlement negotiated before certification); County of Suffolk v. Long Island Lighting Co., 907 F.2d 1295, 1323 (2d Cir. 1990) ("A proffered settlement that is in large part negotiated prior to certification of the class – as occurred herein – is subject to a higher degree of scrutiny than is usual in assessing a settlement's fairness.").

A. The Complete Absence of Discovery Weighs Against Approval of the Settlement

"[A] decision to settle that occurs at too incipient a stage of the proceedings . . . weighs against settlement approval." GM Trucks, 55 F.3d at 810 (emphasis added). The presumption against approval is particularly strong where the parties engaged in no formal discovery. "[C]ourts frequently have ruled that discovery relating to the issue whether a class action is appropriate needs to be undertaken before deciding whether to allow the action to proceed on a class basis." Wright et al., 7AA Federal Practice & Procedure § 1785.3 (3d ed. 2014) (emphasis added). Discovery allows counsel to develop "an adequate appreciation of the merits of the case before negotiating." GM Trucks, 55 F.3d at 813. "The deference afforded counsel should correspond to the amount of discovery completed and the character of the evidence uncovered." Williams v. Vukovich, 720 F.2d 909, 922-23 (6th Cir. 1983). Thus, when no discovery is taken, a court must "question[] whether class counsel could have negotiated in [the] best interests" of absent class members. In re Cmty. Bank of N. Va., 418 F.3d 277, 307 (3d Cir. 2005) (rejecting class settlement). In other words, "achiev[ing] the settlement after little or no discovery... raise[s] a red flag." GM Trucks, 55 F.3d at 806 (emphasis added).

Here, Class Counsel appear to have conducted *no discovery* – none. The absence of even a basic factual record precludes any reasonably valid assessment of the value of the class's claims. Put differently, there is no basis to determine whether the Settlement is fair, adequate, and reasonable. The absence of discovery is particularly glaring because the Complaint alleges fraud and negligent concealment, where the best evidence is likely in the Defendants' hands. The Complaint lists dozens of media reports and facts demonstrating the NFL's cover-up of information and willful dissemination of misinformation regarding the risks of head trauma from football. *E.g.*, Compl. ¶¶ 128-199. Investigation of these facts through discovery of the NFL's

internal files could yield powerful and compelling evidence of the NFL's culpability – strengthening Class Counsel's hand at the negotiating table. Yet Class Counsel settled this case without taking a single deposition and without the NFL producing a single document related to the merits of the underlying claims.

Instead, Class Counsel purport to have "exchanged information" with the NFL during the negotiation, including "expert calculations of damages." Dkt. No. 6073-5 at 43. That is insufficient. Nothing in the record demonstrates that Class Counsel "conducted significant independent discovery or investigations *to develop the merits of their case (as opposed to supporting the value of the settlement)*." *GM Trucks*, 55 F.3d at 814 (emphasis added). In the absence of such discovery, this Court must lack "confidence that the proceedings had advanced to the point that counsel could fairly, safely, and appropriately decide to settle the action." *Id*.

Courts routinely refuse to approve class settlements in the absence of adequate discovery. In *GM Trucks*, for example, the Third Circuit found that the "district court clearly erred in finding that this [*Girsh*] factor weighed in favor of settlement" where the district court failed to "assur[e] that adequate discovery had been taken." 55 F.3d at 814. And in *Mills v. Foremost Insurance Co.*, 511 F.3d 1300 (11th Cir. 2008), the Eleventh Circuit concluded that "the district court's class certification ruling was premature" because of the absence of discovery. *Id.* at 1309; *see also Vinole v. Countrywide Home Loans, Inc.*, 571 F.3d 935, 942 (9th Cir. 2009) ("propriety of a class action cannot be determined in some cases without discovery").

By contrast, when courts have found this *Girsh* factor to weigh in favor of settlement, the settling parties have engaged in far more extensive investigation and discovery than what has

⁶⁰ The actuarial reports have no impact on this *Girsh* factor because that information bears only on "the value of the settlement," not "the merits of [plaintiffs'] case." *GM Trucks*, 55 F.3d at 814.

occurred here. See, e.g., Cendant Corp., 264 F.3d at 235-36 ("extensive discovery," review of produced documents and witness interviews, and retention of a damages expert); In re Warfarin Sodium Antitrust Litig., 391 F.3d 516, 537 (3d Cir. 2004) ("hundreds of thousands of documents ..., numerous depositions, and consultations with experts"); In re Prudential Ins., 148 F.3d 283, 319 (3d Cir. 1998) (review of a "multitude of documents," interviews with hundreds of potential witnesses, and 20 depositions). And cases where courts granted final approval in the absence of formal discovery have similarly involved far more extensive informal investigations than Class Counsel performed in this case. 61 Class Counsel's discovery efforts to date fall well short of the benchmark established by these cases.

Negotiating blindly, Class Counsel entered into the settlement negotiations with nothing more than an uneducated guess as to the merits of the case. They could not "fairly, safely, and appropriately decide to settle the action." *GM Trucks*, 55 F.3d at 814.

B. The NFL's Ability To Withstand a Far Greater Judgment Than That Provided by the Settlement Weighs Against Approval of the Settlement

A defendant's ability to "withstand a judgment for an amount significantly greater" than the proposed settlement weighs against approval. Cendant Corp., 264 F.3d at 240-41 (finding that this factor weighed against settlement when the defendant could "pay significantly more than [the] \$2.85 billion" settlement). Undoubtedly, the NFL can.

⁶¹ See Barani v. Wells Fargo Bank, N.A., No. 12-2999, 2014 WL 1389329, at *5-6 (S.D. Cal. Apr. 9, 2014) (noting "substantial discovery" and "thorough[] investigat[ion]"); In re Processed Egg Prods. Antitrust Litig., 284 F.R.D. 249, 271 (E.D. Pa. 2012) (describing informal discovery of over 3,200 documents that described defendant's "participation in the conspiracy"); Gates v. Rohm & Haas Co., 248 F.R.D. 434, 444 (E.D. Pa. 2008) (noting "dozens of depositions," "hundreds of pages of expert reports," and "hundreds of thousands of pages of documents" produced even though "the parties have not yet officially conducted discovery on the merits").

Although the Monetary Award Fund is no longer capped, lifting the cap is a cosmetic gesture. The settling parties have emphasized repeatedly that they "remain undeterred in their belief that the \$760 million deal originally struck would have been sufficient to compensate all Class Members with valid claims over the term of the Monetary Award Fund." Dkt. No. 6073-5 at 12; *see also* Dkt. Nos. 6167, 6168. And the hurdles imposed on those seeking to file a claim will reduce the value of the Settlement further still. *See* pp. 71-80, *infra*.

The NFL can withstand a judgment many times the amount of the settling parties' own valuation of the Settlement. Last year alone the NFL had annual revenue of more than \$10 billion, 62 earned a reported \$1 billion from licensing, and paid its commissioner more than \$35 million. 63 The NFL's \$950 million TV contract for *one season* of Sunday Night Football would itself cover the cost of the current Settlement. 64 And the NFL projects revenues of \$25 billion by 2027. 65 Moreover, the NFL has not disclosed how much it, rather than its insurers, would have to pay to settle these claims. *See Ortiz v. Fibreboard Corp.*, 527 U.S. 815, 863-64 (1999) (vacating settlement, in part because the district court failed to evaluate the fairness of the settlement in light of the available assets of both the defendant and its insurers).

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⁶² Schrotenboer, *NFL Takes Aim at \$25 Billion, But At What Price?*, USA Today (Feb. 5, 2014), http://www.usatoday.com/story/sports/nfl/super/2014/01/30/super-bowl-nfl-revenue-denver-broncos-seattle-seahawks/5061197/ (attached as Exhibit 41).

⁶³ Wilson, *NFL Paid Roger Goodell \$35.1 Million Last Year*, CBSSports.com (Feb. 14, 2014), http://www.cbssports.com/nfl/eye-on-football/24443392/report-nfl-paid-roger-goodell-351-million-last-year (attached as Exhibit 42).

⁶⁴ Futterman *et al.*, *NFL: The League that Runs TV*, Wall St. J. (Dec. 15, 2011), http://online.wsj.com/article/SB10001424052970204026804577098774037075832.html (attached as Exhibit 43).

⁶⁵ See Kaplan, Goodell Sets Revenue Goal of \$25B by 2027 for NFL, Sports Business Journal (Apr. 5, 2010), http://www.sportsbusinessdaily.com/Journal/Issues/2010/04/20100405/This-Weeks-News/Goodell-Sets-Revenue-Goal-Of-\$25B-By-2027-For-NFL.aspx (attached as Exhibit 44).

C. The Negative Reaction of the Class Weighs Against Approval of the Settlement

Inquiry into the reaction of the class generally looks at "the number and vociferousness of the objectors" and opt-outs. *GM Trucks*, 55 F.3d at 812. From the outset, the reaction of the class has been negative:

- Chidi Ahanotu: "The key part of this will be the people who determine who qualifies and who's eligible. . . . If it's like the NFL's disability benefit program, *this isn't a win for the players*. That panel denies most requests." 66
- Kevin Mawae: "Basically, for the cost of their least valuable team, the NFL was able to remove a huge monkey off their back. . . . At the end of the day, it's a very small price to pay considering the negative outcome that could have happened to the NFL if the players had taken this to court." 67
- Leroy Hoard: "They (the NFL) put a big settlement number out there, but guess what? They say you have to qualify, how easy will they make that?" 68
- Wade Smith: "At the surface it looks like a good deal. But in the long run I don't think it is. That's usually how it works when it comes to players and ownership." 69
- Dorsey Levens: "This is a great victory for them [the NFL]. I didn't understand how they got off so lightly."⁷⁰

After this Court *sua sponte* rejected the initial settlement, criticism of the settlement agreement continued. Within two weeks of this Court's Order, for example, the Seau family

⁶⁶ Banks, Former Players: Devil Is in the Details with NFL Concussion Settlement, SI.com (Aug. 29, 2013) (emphasis added), http://www.si.com/nfl/2013/08/29/nfl-concussion-lawsuit-settle ment-player-reaction-kevin-mawae (attached as Exhibit 45).

⁶⁷ Futterman & Clark, *Deal in Concussion Suit Gives NFL a Big Victory*, Wall St. J. (Aug. 29, 2013), online.wsj.com/article/SB10001424127887324463604579042980915590474.html (attached as Exhibit 46).

⁶⁸ ESPN.com, *Reaction to the Concussion Deal* (Aug. 30, 2013) ("ESPN Reactions"), espn.go.com/nfl/story/_/id/9612672/reaction-nfl-concussion-settlement (attached as Exhibit 47).

Wolfley, *Dorsey Levens Rips Settlement of Concussion Lawsuit Against NFL*, Milwaukee Journal Sentinel (Sept. 18, 2013), http://www.jsonline.com/sports/dorsey-levens-rips-settlement-of-concussion-lawsuit-against-nfl-b99101255z1-224335851.html (attached as Exhibit 48).

filed a statement noting their objections to the settlement. *See* Dkt. No. 5695. Another 214 plaintiffs filed shortly thereafter, seeking "thorough analysis of the proposed settlement." Dkt. No. 5778 at 1-2.

After preliminary approval, class members have maintained their opposition. The Seau family has continued its criticism.⁷¹ Joe DeLamielleure is "going to tell everyone I know to object."⁷² NFL legend and Hall of Famer Emmitt Smith called the settlement "nothing."⁷³ Class members are already filing objections. *See* Dkt. No. 6175. Indeed, the settling parties' actuaries estimate that as much as *40% of the class will not participate in the Settlement* for one reason or another. Dkt. No. 6167 at 38; Dkt. No. 6168 at 33.

All this criticism indicates that the number of opt-outs and objectors will be high. But even if the number of opt-outs and objectors comprises only a small percentage of the class, that would not support approval because the class notice "was not neutral and it did not provide a truthful basis for deciding whether to opt out." *Eubank*, 753 F.3d at 728 (holding small number of objectors did not weigh in favor of settlement); *accord GM Trucks*, 55 F.3d at 813 (lack of objectors did not weigh in favor of approval because the "notice largely defeats the potential for objection since" it was incomplete); *see also* pp. 38-55, *supra*.

Moran, *Seau Family Says "No" to NFL Settlement*, U-T San Diego (Sept. 3, 2014), http://www.utsandiego.com/news/2014/sep/03/seau-family-says-no-to-nfl-settlement/ (attached as Exhibit 49).

Fenno, *Hall of Famer Joe DeLamielleure Will Object to NFL Concussion Deal*, The L.A. Times (Sept. 4, 2014), http://www.latimes.com/sports/sportsnow/la-sp-sn-nfl-concussion-deal-joe-delamielleure-20140904-story.html (attached as Exhibit 50).

⁷³ Interview with Emmitt Smith, *In Depth with Graham Bensinger*, at 3:03 (Sept. 18, 2014), http://sports.yahoo.com/video/emmitt-smith-20k-concussion-settlement-110000539.html.

D. The Risks of Establishing Liability and Damages Weigh Against Approval of the Settlement

The absence of even a basic factual record – because no discovery has occurred – precludes a complete assessment of the risks of establishing liability and damages. However, the public information that *is* available demonstrates that the class's claims are strong and the NFL's defenses are weak.

1. Even Without Discovery, Publicly Available Information Shows the Strength of Plaintiffs' Claims

The publicly available facts show that the NFL was aware of its responsibility to protect its players, knew or should have known that its policies and conduct were leading to widespread exposure to neurodegenerative diseases, and that – far from helping protect its players from brain trauma – the NFL sought to quash any research drawing a connection between the two. *See* pp. 5-10, *supra*.

a. The NFL Assumed a Duty of Care To Guard Player Health and Safety

The NFL has publicly represented that "[s]ince its earliest days, the league has continuously taken steps to ensure that the game is played as fairly as possible without unnecessary risk to its participants, including making changes and enhancements to game safety rules." Compl. ¶ 69; see also id. ¶¶ 73-81. It formed an MTBI Committee whose ostensible purpose was to study links between head injuries and neurodegenerative diseases. But the Committee's supposed research – which was disseminated widely – repeatedly found no links between the two and stood in stark contrast to research by the scientific community.

b. Medical Studies Show That the NFL Knew or Should Have Known of the Link Between MTBI and Brain Damage, Particularly the Onset of CTE

Countless studies, dating back to the 1920s, show that both concussive and sub-concussive head trauma leads to, among other things, cognitive impairment, memory loss, and depression. In recent years, these studies have focused on the presence of CTE in athletes, particularly those who had sustained repeated head trauma. In 2002, Dr. Bennet Omalu, a forensic pathologist, identified CTE in the brain of former Pittsburgh Steelers' center Mike Webster. Dr. Omalu identified CTE again in 2005 and 2006 in the brains of former players Terry Long and Andre Waters – both of whom committed suicide. And numerous medical studies – issued at approximately the same time as the NFL's misinformation campaign – have addressed the issue of CTE and/or cognitive impairment arising from concussions sustained during football.

⁷⁴ See, e.g., Kain, It's Just a Concussion: The National Football League's Denial of a Causal Link Between Multiple Concussions and Later-Life Cognitive Decline, 40 Rutgers L.J. 697, 701-02 & n.26 (2009); Roberts, Brain Damage in Boxers: A Study of the Prevalence of Traumatic Encephalopathy Among Ex-Professional Boxers 61 (1969); Busse & Silverman, Electroencephalographic Changes in Professional Boxers, 149 J.A.M.A. 1522 (1952) (attached as Exhibit 51); Martland, Punch Drunk, 91 J.A.M.A. 1103 (1928) (attached as Exhibit 52).

⁷⁵ Fainaru-Wada & Fainaru, *League of Denial*, *supra*, at 158, 163.

⁷⁶ Schwarz 2007, supra.

⁷⁷ See, e.g., McKee et al. 2013, supra, at 59; McKee et al., Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury, 68 J. Neuropathology & Experimental Neurology 709, 710 (2009) (attached as Exhibit 53); Cantu, Chronic Traumatic Encephalopathy in the National Football League Player, 61 Neurosurgery 223 (2007) (attached as Exhibit 54); Guskiewicz et al., Association Between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players, 57 Neurosurgery 719 (2005) (attached as Exhibit 55); Omalu et al., Chronic Traumatic Encephalopathy in a National Football League, 57 Neurosurgery 128 (2005) (attached as Exhibit 56); Omalu et al., Chronic Traumatic Encephalopathy in a National Football League Player: Part II, 59 Neurosurgery 1086 (2006) (attached as Exhibit 57).

c. The NFL Actively Worked To Conceal the Correlation Between MTBI and Brain Damage

The NFL's MTBI Committee devoted its resources to artificially creating "scientific" papers of its own that directly contradicted decades of research on brain trauma. For example, in 2005, the MTBI Committee concluded that returning to play after sustaining a concussion "does not involve significant risk of a second injury either in the same game or during the season."⁷⁸ In another paper, the MTBI Committee represented: "mild TBIs in professional football are not serious injuries"; "[i]n players with four or more concussions there was a greater chance of personality change, and fatigue, but the number did not reach statistical significance"; "this 6year study indicates that no NFL player experienced second-impact syndrome, chronic cumulative injury, or chronic traumatic encephalopathy from repeated injuries;" "players who become asymptomatic and have normal results on examinations performed at any time after injury, while the game is still in progress, have been and can continue to be safely returned to play on that day."⁷⁹ In a 2007 interview on HBO's Real Sports, moreover, then-NFL MTBI Committee co-chair Ira Casson insisted there was no link between multiple head injuries in professional football players and such conditions as depression, dementia, and early-onset Alzheimer's.80

These representations were not outliers. In its 2007 concussion guidelines, the NFL represented: "Current research with professional athletes has shown that you *should not be at*

⁷⁸ CNN Library, *NFL Concussions Fast Facts*, CNN U.S. (July 21, 2014), http://www.cnn.com/2013/08/30/us/nfl-concussions-fast-facts/ (attached as Exhibit 58).

⁷⁹ Pellman et al., Concussion in Professional Football: Summary of the Research Conducted by the National Football League's Committee on Mild Traumatic Brain Injury, 21 Neurosurgery Focus 1, 9-10 (2006) (emphasis added) (attached as Exhibit 59).

⁸⁰ Hruby, *The Case Against the NFL*, The Post Game (Feb. 29, 2012), www.thepostgame.com/blog/hruby-tuesday/201202/case-against-nfl (attached as Exhibit 60).

greater risk of further injury once you receive proper medical care for a concussion and are free of symptoms," that "[c]urrent research with professional athletes has not shown that having more than one or two concussions leads to permanent problems if each injury is managed properly," and that "there is no magic number for how many concussions is too many." In January 2010, during a House Judiciary Committee hearing, Dr. Casson further denied a link between repeat head impacts and long-term brain damage. 82

At the very least, publicly available information establishes that, despite the absence of discovery, Plaintiffs' claims are viable.

2. Discovery Would Have Allowed Class Counsel To Overcome – or at Least Understand – the Supposed "Stiff and Complex Challenges" to a Successful Suit

The absence of discovery also hampers class members' abilities to evaluate the strength of the NFL's defenses. *See* pp. 56-59, *supra*. In moving for preliminary approval of the settlement, Class Counsel focused on the "stiff and complex challenges" they purportedly faced in surmounting Defendants' defenses: preemption, causation, statute of limitations, assumption of the risk, and "other defenses." Dkt. 6073-5 at 61-71. Although Class Counsel claim that whether they could satisfy their burden of proof was a "significant consideration" in settling, *id.*, that is a red herring. Whether a burden of proof is met is a question of fact, and Plaintiffs developed no facts through discovery. Had they done so, they may not have considered the

National Football League, *NFL Outlines for Players Steps Taken to Address Concussions*, NFL.com (Aug. 14, 2007) (emphasis added), http://www.nfl.com/news/story/09000d5d8017 cc67/article/nfl-outlines-for-players-steps-taken-to-address-concussions (attached as Exhibit 61).

⁸² Legal Issues Relating to Football Head Injuries (Part I & II): Hearings Before the H. Comm. on the Judiciary, 111th Congress 334-35 (2010) (statement of Ira R. Casson, M.D.), http://www.gpo.gov/fdsys/pkg/CHRG-111hhrg53092/pdf/CHRG-111hhrg53092.pdf.

challenges so "stiff and complex." But even based on the information currently available, the NFL's claimed defenses are weak.

Preemption. Class Counsel contend that preemption under § 301 of the Labor Management Relations Act (LMRA), 28 U.S.C. § 185, presents a "significant" legal challenge for Plaintiffs in light of the NFL Defendants' referenced collective-bargaining agreements (CBAs). Dkt. No. 6073-5 at 61-64. But § 301 only preempts "claims founded *directly* on rights created by collective-bargaining agreements," or claims "*substantially dependent* on analysis of a collective-bargaining agreement." *Caterpillar, Inc. v. Williams*, 482 U.S. 386, 394 (1987) (emphasis added) (quotation marks omitted) (former employees' claims against former employer were not preempted because claims arose out of individual employment contracts and did not touch on CBA provisions).

In fact, in *Green v. Arizona Cardinals Football Club*, the district court, relying on *Caterpillar*, recently held that the claims of retired NFL players against the Arizona Cardinals for brain injuries resulting from TBI *were not precluded by the CBA*. *Green v. Ariz. Cardinals Football Club, LLC*, No. 14-CV-461, 2014 WL 1920468, at *3 (E.D. Mo. May 14, 2014). The court's reasoning holds true here: Preemption is not triggered where a dispute only "tangentially involv[es] a provision of a [CBA]." *Allis-Chalmers Corp. v. Lueck*, 471 U.S. 202, 211 (1985). Stated differently, "section 301 does not preempt state law claims merely because the parties involved are subject to a CBA and the events underlying the claim occurred on the job." *Williams v. Nat'l Football League*, 582 F.3d 863, 874 (8th Cir. 2009). What matters is whether the plaintiffs' claims turn on rights that are actually set forth in a CBA provision or that "'require interpretation or construction of the CBA'" itself. *Green*, 2014 WL 1920468, at *3 (quoting *Williams*, 582 F.3d at 876) (rejecting preemption argument on ground that alleged NFL CBAs

were not the source of players' claims of negligence, misrepresentation, and fraudulent concealment).

Plaintiffs' claims here turn on factual questions about the NFL's conduct – what actions or representations it did or did not perform and when and why it decided to perform them. For example: When did the NFL first learn of the connection between MTBI and neurodegenerative disease? What data did the NFL collect? How and why did it craft its public statements on concussions? Discovery is needed before making any realistic assessment as to the "challenges or obstacles" Plaintiffs might face regarding preemption.

Causation. Class Counsel claim they face "significant legal impediments surrounding [their] ability to prove causation and obtain verdicts in the absence of a settlement." Dkt. No. 6073-5 at 64. But "[p]roximate cause requires only 'some direct relation between the injury asserted and the injurious conduct alleged,' and excludes only those 'link[s] that are too remote, purely contingent, or indirect.'" Staub v. Proctor Hosp., 131 S. Ct. 1186, 1192 (2011). Unless the NFL Defendants' conduct was a "trivial contribution" to the putative class members' "cause of harm," the NFL Defendants' conduct is a proximate cause of the class members' injuries. Restatement (Third) of Torts: Phys. & Emot. Harm § 36 (2010).

Class Counsel are wrong to cede any ground to this defense without obtaining discovery into the Defendants' conduct. When the NFL first learned of the connection between head trauma and neurodegenerative disease, what studies it undertook concerning this information, and how and why it crafted its public statements concerning concussions, are questions that should be pursued through discovery to address the purported causation "impediment."

Statute of Limitations. Class Counsel contend their claims faced "a significant potential risk" of dismissal in light of the "serious challenge" presented by a statute of limitations. Dkt.

6073- at 65. This professed concern ignores the doctrine of fraudulent concealment, which "tolls the statute of limitations where 'through fraud or concealment the defendant causes the plaintiff to relax vigilance or deviate from the right of inquiry.'" *Mest v. Cabot Corp.*, 449 F.3d 502, 516 (3d Cir. 2006) (whether defendants made misrepresentations and the nature of any misrepresentations is relevant to determining if fraudulent concealment tolled limitations period).

Significantly, Class Counsel urged that a statute of limitations defense should fail on this very ground in other litigation. *See Finn* Compl. ¶¶ 144-148 (the "applicable statute of limitations is tolled because Defendant's fraudulent concealment of the dangers and adverse effects of head injuries made it impossible for Plaintiffs to learn of the hazards to their health"). The question is whether a defendant undertook some "affirmative and independent act of concealment that would prevent the plaintiff from discovering the injury[,] despite the exercise of reasonable diligence." *Bohus v. Beloff*, 950 F.2d 919, 925 (3d Cir. 1991). Rather than answer that factual question through evidence developed in discovery to negotiate a settlement that compensates all injured class members, Class Counsel punted by excluding all class members who died before January 1, 2006, unless the claimant can demonstrate that the statute of limitations would not apply. Settlement § 6.2(b)

Assumption of the Risk. Class Counsel argue that an "assumption-of-risk" defense also potentially blocks Plaintiffs' claims. Dkt. No. 6073-5 at 67-70. But the assumption of risk "doctrine is very narrow," limited only to circumstances where it is clear that "the 'nature and extent' of the risk were 'fully appreciated' and that the plaintiff voluntarily proceeded to face that risk." Barnes v. Am. Tobacco Co., 984 F. Supp. 842, 869 (E.D. Pa. 1997). The retired players unquestionably assumed certain bodily risks, but they did not consent to face the types of harm alleged here – harm concealed from them by Defendants. See, e.g., Murphy v.

Steeplechase Amusement Co., 250 N.Y. 479, 482-83 (1929) ("One who takes part in [] a sport accepts the dangers that inhere in it so far as they are obvious and necessary, . . . [but a] different case would be here if the dangers inherent in the sport were obscure or unobserved, or so serious as to justify the belief that precautions of some kind must have been taken to avert them.").

Class Counsel pled facts – for which they presumably had a good-faith basis – that would easily defeat an assumption of the risk defense. The evidence supporting those allegations has not been developed through discovery.

Statutory Employer. Class Counsel also state that the NFL Defendants "may argue they are similarly situated to a general contractor with respect to the injured players, and the injured players are akin to the employees of subcontractors." Dkt. No. 6073-5 at 71. However, "very great care . . . must be exercised before allowing an employer to avoid his liability at common law by asserting that he is a statutory employer." Stipanovich v. Westinghouse Elec. Corp., 210 Pa. Super. 98, 106 (1967). In the Third Circuit, defendants must identify "an owner, a principal contractor[,] and a subcontractor" for the defense to apply; a party "cannot be both the owner (or in the position of owner) and statutory employer at the same time." Pozza v. United States, 324 F. Supp. 2d 709, 712 (W.D. Pa. 2004) (citing Jamison v. Westinghouse Elec. Corp., 375 F.2d 465, 469 (3d Cir. 1967) (emphasis added)). If the defense were to be asserted, discovery would be needed into the NFL, the individual teams, and the teams' owners to examine their corporate structure and contractual relationships.

* * * * *

In sum, the absence of discovery makes it impossible for class members to accurately assess the risks of establishing liability and damages. But even on the information that is

available, class members have strong arguments that the NFL is liable and that damages can be proven.

E. The Best Possible Recovery and the Risks of Litigation Weigh Against Approval of the Settlement

A court must examine "the value of the settlement itself to determine whether the decision to settle represents a good value for a relatively weak case or a sell-out of an otherwise strong case." *GM Trucks*, 55 F.3d at 806. This Settlement is a sell-out. The Settlement terms do include multi-million dollar maximum awards and an uncapped monetary award fund. But that generosity is illusory. From the MTBI-related injuries that go completely uncompensated to the offsets that reduce individual awards and the procedural maze that claimants must navigate to receive payment, the Settlement is designed to dramatically reduce the number of claims on which the NFL must actually pay. Where, as here, the "real value" of a settlement to the class falls well short of its ostensible face value, the settlement is not reasonable in light of the "best possible recovery" and the attendant risks of litigation. *See GM Trucks*, 55 F.3d at 807-10.

1. The Proffered Value of the Settlement Is Illusory Because the Settlement Leaves Many Class Members Without Compensation for Their MTBI-Related Diseases

A settlement is not the "best possible recovery" where "some segments of the class are treated differently from others." *GM Trucks*, 55 F.3d at 808; *see Vassalle v. Midland Funding LLC*, 708 F.3d 747, 755 (6th Cir. 2013) ("disparity in the relief afforded under the settlement to the named plaintiffs, on the one hand, and the unnamed class members, on the other, [makes] the settlement unfair"). "In the class action context, 'the relief sought in the complaint' serves as a useful benchmark in deciding the reasonableness of a settlement." *GM Trucks*, 55 F.3d at 810. CTE is at the heart of the Class Action Complaint and was a driving force of this lawsuit. *See* pp. 31-32, *supra*. The total failure to compensate current and future cases of CTE shows that the

Settlement is not reasonable in light of the best possible recovery. *See GM Trucks*, 55 F.3d at 810 (settlement not reasonable where "coupons offered by [defendant] simply do not address the safety defect that formed the central basis of the amended complaint filed barely four months before the settlement"). 83

The 75% offset for stroke and TBI further reduces the actual value of the settlement relative to the best possible recovery. Both Class Counsel and the NFL accounted for the 75% offset in their actuarial estimates evaluating the settlement. *See* Dkt. No. 6167 at 18-19; Dkt. No. 6168 at 37-38. Both relied on the incidence of stroke in the general population. Class Counsel assumed that 9.1% of Alzheimer's patients and 8.4% of dementia patients would suffer a stroke before the onset of disease. Dkt. No. 6167 at 18-19. The NFL assumed a rate of stroke at 4.5%. Dkt. No. 6168 at 37. But any reliance on figures for the general population is seriously flawed. Former NFL players likely face a *higher risk* of stroke precisely because of the head injuries they suffered in the NFL. *See* pp. 33-34, *supra*.

The stroke offset also disproportionately burdens some class members more than others.

African-Americans are 1.3 times more likely to have a stroke than others.

84 Yet the Settlement

The Settlement is not reasonable even according to Class Counsel's own flawed figures. Although CTE is likely to be the most common neurocognitive disease suffered by the class, Class Counsel identified only 46 cases of CTE from among 1,700 class members who have died. See Dkt. No. 6167 at 3, 5. Applying that absurdly low 2.7% rate of CTE across the 19,400 class members living today, id. at 3, would indicate that there will be 525 more cases of CTE in the future. Accepting the settling parties' own valuation of CTE as a \$1.44 million injury (after discounting for age at time of diagnosis and years played, Dkt. 6167 at 8 tbl. 2-4), the total value of future CTE claims would still be \$756 million. But the Settlement reduces that figure to zero. On that basis alone, the Settlement is unreasonable. See Eubank, 753 F.3d at 726 ("A class recovery of little more than \$1 million is a long way from the \$90 million that the district judge thought the class members likely to receive were the suit to be litigated.").

⁸⁴ See Ayala et al., Racial/Ethnic Disparities in Mortality by Stroke Subtype in the United States, 1995-1998, 154 Am. J. of Epidemiology 1057 (2001) (attached as Exhibit 62).

severely reduces recovery for an event that disproportionately affects a significant percentage of the settlement class.

The Settlement also provides no credit for seasons played in NFL Europe, notwithstanding that the risk of injury in NFL Europe did not differ from the risk in the NFL in any meaningful way. *See* pp. 35-37, *supra*; Morey Decl. ¶ 6. Neither the NFL nor Class Counsel estimate the number of class members whose service in NFL Europe rather than the NFL reduced their overall recovery. But one collection of football statistics identifies *over 3,600 players* who spent time in the league. 85 Thus, the failure to credit seasons played in NFL Europe could affect a large number of class members.

In short, the "fact that the . . . settlement benefits certain groups of the class more than others" weighs against final approval, and demonstrates that the settlement was "a sell-out of an otherwise strong case." *GM Trucks*, 55 F.3d at 806, 808.

2. The Proffered Value of the Settlement Is Illusory Because It Sets an Unreasonably High Bar To Qualify for Dementia

The Settlement sets an unreasonably high bar to qualify even for Level 1.5 dementia. To do so, a class member must be unable to function independently at a job, shopping, volunteer or social activities; must be unable to complete difficult chores or complicated hobbies; *and* must require prompting to engage in personal care such as dressing, bathing, and using the bathroom. Stern Decl. ¶ 47. Junior Seau and Dave Duerson – two NFL greats who killed themselves and were found to have CTE – reportedly experienced "years of significant changes in mood and behavior, including depression, hopelessness, aggression, and poor impulse control." *Id.* ¶ 35. "Based on public reports of their functioning by their family members and friends," however, "it

⁸⁵ See NFL Europe/WLAF Player Register, *The Football Database*, http://www.footballdb.com/nfl-europe/nfleplayers.html (accessed Sept. 24, 2014).

is unlikely that their cognitive skills were impaired to the degree of meeting the criteria for Level 1.5 or Level 2 Neurocognitive Impairment." *Id*.

3. The Proffered Value of the Settlement Is Illusory Because the Baseline Assessment Program Is Underinclusive

The Baseline Assessment Program (BAP) offers far less value than the Settlement proclaims. Class Counsel agreed to a \$75 million cap on the baseline assessment fund without any evidence that the capped amount was adequate. Indeed, Class Counsel's actuaries made no projections about the estimated draw on the BAP, see Dkt. No. 6167, although the NFL's actuary did, see Dkt. No. 6168 at 42-44. Class Counsel thus either agreed to a cap without any assessment of whether the fund was adequate or agreed to a cap on the basis of representations made by their adversary across the negotiating table. Either way, Class Counsel did not fulfill their fiduciary obligation to the class.

The NFL's analysis of the adequacy of the BAP fund, moreover, is seriously flawed. The actuaries were "*instructed to assume* that, for players diagnosed with a Level 1 diagnosis" of dementia, "the cost of further testing, treatment, and related drug therapy would not exceed \$35,000 per player." Dkt. No. 6168 at 43 (emphasis added). But the actual cost of treating dementia can reach \$56,000 *a year*. A BAP fund that ignores actual data and includes a cap based on an obviously flawed assumption is grossly inadequate and will run out long before the end of a Settlement that is supposed to last for 65 years.

The BAP, moreover, is flawed as a matter of design and will deprive deserving class members of compensation for their MTBI-related injuries. *The BAP does not even test at all for*

⁸⁶ Zorumski & Rubin, *The Financial Cost of Dementia*, Psychology Today (Oct. 10, 2013), http://www.psychologytoday.com/blog/demystifying-psychiatry/201310/the-financial-cost-dementia (attached as Exhibit 63).

the mood and behavioral disorders that plague many individuals with CTE. Stern Decl. ¶¶ 31, 45. And many class members entitled to compensation under the Settlement will not receive a diagnosis of dementia under the BAP. Administering the complete battery of tests "would take approximately five hours without any break." Stern Decl. ¶ 44. There is no justification for a five-hour test. The testing protocols prescribed by the Settlement are generally considered inappropriate for the evaluation of individuals with neurodegenerative diseases. *Id.* ¶ 43. As Dr. Stern explains, a five-hour test without any break would "result in refusals to complete the evaluation" by many individuals suffering from dementia who would otherwise be compensated under the Settlement. *Id.* ¶ 44.

The testing battery also incorporates several effort and performance metrics that are inappropriate for use on individuals suffering from the levels of cognitive impairment compensated under the Settlement. Stern Decl. ¶¶ 45-46. Effort metrics are typically included in a neuropsychological test battery to screen for individuals whose low scores result from a lack of effort rather than diminished cognitive ability. "[B]ecause patients with dementia are so impaired cognitively," however, "they may perform poorly on the effort test due to their actual cognitive impairment rather than poor effort." *Id.* ¶ 48.

In short, because the testing battery prevents deserving class members with valid claims from obtaining the awards to which they are entitled under the Settlement, the Settlement is unreasonable in light of the best possible recovery.

4. The Proffered Value of the Settlement Is Illusory Because the Settlement Requires Class Members To Navigate a Complex Procedural Maze To Secure Recovery

To receive *any* recovery, class members must navigate a complex and burdensome administrative process that appears designed to decrease the cost of the Settlement to the NFL. Because many cognitively impaired class members may find themselves unable to steer through

this procedural thicket, their valid claims will be denied or reduced, limiting the NFL's total payout under the Settlement and diminishing the value of the Settlement relative to the best possible recovery. *See GM Trucks*, 55 F.3d at 808 (holding concerns about "real value" of settlement weighed against final approval); *see also Eubank*, 753 F.3d at 726 (reversing approval of settlement where "restrictions that [defendant] was allowed to place on the settlement would, if upheld, enormously reduce the class members' recovery"). Like the class settlement recently rejected in *Eubank*, 753 F.3d at 724, the Settlement "strews obstacles in the path of any" class member seeking recovery by imposing requirements and deadlines that, if unsatisfied, reduce or completely bar recovery.

a. Class Members Are Required To "Opt In" and Meet Arbitrary Examination Deadlines

Class members have 180 days to register with the Claims Administrator, essentially requiring class members to opt in even though they never opted out of the class in the first place. Any class member who fails to do so is *ineligible for any benefits*, even though their claims are released. Settlement § 4.2(c). And even those class members who do register in a timely fashion may find themselves battling the NFL from the outset – the NFL can "challenge" a Notice of Registration Determination in favor of a class member. *Id.* § 4.3(a)(iii).

Some class members, moreover, must undergo baseline assessment examinations by arbitrary deadlines. For example, any class member who has not received a qualifying diagnosis by the Settlement's effective date must undergo the baseline assessment (1) within two years after the BAP begins if the class member is 43 or older on the effective date; or (2) by the earlier of his 45th birthday or within 10 years after the BAP begins, if the class member is younger than 43 on the effective date. Settlement § 5.3. Class members who forgo the baseline assessment suffer a 10% offset if they later develop a qualifying diagnosis. *Id.* §§ 5.4, 6.7(b)(iv).

b. Class Members Are Required To Prepare and File an Unreasonably Complex and Ambiguous "Claim Package"

The claims process erects other barriers to recovery. Class members must file an extensive "Claim Package" within two years of receiving a qualifying diagnosis. Settlement §§ 8.2(a), 8.3(a)(i). But Class Counsel have not even disclosed the proposed claim form and instructions for submitting the claims packet. Class members are left to trust Class Counsel that the claim form they negotiate will help, rather than hinder, class members' ability to file valid claims. If the rest of the claims process is any indication, class members should be skeptical.

It gets worse. Class members are required to provide "objective evidence beyond [a] sworn statement" of NFL employment and participation in more than one eligible season. Settlement § 9.1(a)(i). Class members who cannot produce such evidence are limited to compensation for one eligible season (which results in an 80% offset, *id.* § 6.7(b)(i)(8)). *Id.* There is no possible justification for this procedural hurdle because *the NFL itself has this data*. The NFL tracks player statistics as far back as 1920, including number of seasons played. As this requirement demonstrates, the claims process is meant to thwart rather than facilitate payments under this purportedly uncapped Settlement.

Once a claim is submitted, moreover, the Claims Administrator can investigate and "request additional documentation." Settlement § 8.6(a). A class member must supply that documentation "in order to claim a Monetary Award." *Id.* Otherwise, his claim will be rejected.

The process of obtaining a qualifying diagnosis is also burdensome. After the effective date of the Settlement, a qualifying diagnosis can be made only by "Qualified MAF Physicians."

⁸⁷ See, e.g., NFL.com, *Players*, http://www.nfl.com/player/georgehalas/2515602/profile (entry for "George Halas" showing "10 seasons" of "experience" from 1920 to 1929) (attached as Exhibit 64).

Settlement § 6.3(b). To receive that designation, physicians must "be approved by Co-Lead Class Counsel and Counsel for the NFL Parties." *Id.* § 6.5(a). The Settlement, moreover, contains no hardship provisions for individuals who may live far away from any Qualified MAF Physician or who may, because of their medical condition, be unable to travel long (or even short) distances to a Qualified MAF Physician. To the contrary, the Settlement provides that "[t]o the extent a Retired NFL Football Player is examined by a Qualified MAF Physician, such visit and examination shall be at the Retired NFL Football Player's own expense." *Id.* § 6.5(a). 89

Class members whose claims are denied may appeal, but only after paying a \$1,000 fee (which is refundable if the appeal is successful). Settlement § 9.6(a). But the NFL may appeal an unlimited number of claim determinations without paying any fee. *Id.* § 9.6(b).⁹⁰ Class members who appeal must "present evidence in support of their appeal" and satisfy a "clear and convincing evidence" standard to prevail. *Id.* §§ 9.7(a), 9.8. Briefing, however, is limited to five pages. *Id.* § 9.7(a). By affording the NFL unlimited appeals and by requiring class members to pay to appeal while operating under unreasonable procedural requirements, the Settlement

⁸⁸ The Settlement also hampers the ability of opt-outs to prosecute their claims against the NFL even if the Settlement is approved. Qualified MAF Physicians, Qualified BAP Providers, and members of the Appeals Advisory Panel and Appeals Advisory Panel Consultants are all prohibited from serving as a consultant or expert witness against the NFL in a concussion-related case; medical professionals who are serving in such a capacity, moreover, are ineligible for appointment to any of those positions. Settlement §§ 5.7(a)(ii), 6.5(b).

That requirement may discourage many players from even seeking out the qualifying diagnosis. Within two years of retirement, 78% of former NFL players are under financial stress. Torre, *How (and Why) Athletes Go Broke*, Sports Illustrated (Mar. 23, 2009), www.si.com/vault/2009/03/23/105789480/how-and-why-athletes-go-broke (attached as Exhibit 65).

⁹⁰ The initial settlement, by contrast, limits the NFL to ten appeals per year. *See* Dkt. No. 5634-2 § 9.6(b). It also required the NFL to pay up to \$2,000 in attorneys' fees and costs if it lost the appeal. *Id.* These provisions were eliminated from the current Settlement.

establishes an asymmetric appellate system tilted decidedly in favor of the NFL and against the class. 91

c. Class Members Are Subject to Additional Arbitrary Procedures That Will Limit Compensation

The Settlement imposes a series of so-called "anti-fraud" provisions that will, in practice, operate as "anti-payment" provisions. The Claims Administrator must audit 10% of all applicants each month. Settlement § 10.3(c). The NFL, moreover, can "at any time" request an audit to verify claims submitted by class members. *Id.* § 10.3(a). Auditors may demand additional information and documents from the class member including all medical records and a list of all health care providers seen in the past five years, among others. *Id.* § 10.3(e). Even partial non-compliance with an auditor's demand requires denial of the claim "without right to an appeal." *Id.* § 10.3(b)(ii).

* * * * *

This complex procedural framework is a transparent attempt to minimize the cost of the settlement to the NFL – a consideration of tremendous importance now that the Settlement is purportedly uncapped. The lowest tiers of compensation from the Monetary Award Fund require a class member "to be so severely impaired in several areas of cognitive functioning that they

[.]

The claims administration process is at risk of operating in a manner similar to current, flawed disability programs jointly administered by the NFL and the NFLPA. Just 34% of the applications submitted for temporary and permanent disability are approved in the initial stage. Halchin, Former NFL Players: Disabilities, Benefits, and Related Issues, Congressional Research Service 82 (2008) (attached as Exhibit 66). Those disability programs, moreover, have been heavily criticized for improperly denying meritorious claims. See id. at 76-77 (quoting Leahy, The Pain Game, Washington Post Magazine, at 10, 23 (Feb. 3, 2008)); see also Rosenberg, "Permanently Disabled," Harrison Fighting for Benefits NFL Took Away, Sports Illustrated (Jan. 29, 2014), http://www.si.com/nfl/2014/01/29/dwight-harrison-nfl-pension (attached as Exhibit 67); O'Keefe, Still Plenty of Skeptics After NFL Reaches New Deal with Players to Settle Concussion-Related Lawsuit, N.Y. Daily News (June 28, 2014), http://www.nydailynews.com/sports/football/score-nfl-deny-issues-article-1.1847588 (attached as Exhibit 68).

would require assistance in many activities of daily living (in Level 1.5) or be almost fully dependent on another person for most activities of daily living, such as bathing and toileting (for Level 2.0)." Stern Decl. ¶ 47. Someone laboring under such impairment has little hope of navigating the procedural morass required to claim payment under the Settlement.

Class Counsel certainly could have negotiated a simpler payment process. They did so for themselves – they will receive their \$112.5 million payment within 60 days after the Settlement takes effect. Settlement § 21.2. Yet their clients – many suffering serious cognitive impairment – will be left wandering through an administrative maze that allows the NFL to say "gotcha" at every turn.

Courts have refused to approve settlements with benefits that are illusory in light of the procedural difficulty to realize them. *See Eubank*, 753 F.3d at 724-25 (rejecting settlement that "strew[ed] obstacles in the path of any" class member); *In re Dry Max Pampers Litig.*, 724 F.3d 713, 718-19, 721 (6th Cir. 2013) (rejecting class settlement, in part, due to an onerous claims process); *Walter v. Hughes Commc'ns, Inc.*, No. 09-2136, 2011 WL 2650711, at *14 (N.D. Cal. July 6, 2011) (rejecting class settlement where "[m]any hurdles stand between a class member and the receipt of . . . payment" and claim form was "unnecessarily complex," "confusingly arranged," and "invites user error"). The Court should do so here.

5. Other Factors Demonstrate That the Value of the Settlement Is Unreasonable in Light of the Best Possible Recovery

Several other factors demonstrate the unreasonableness and inadequacy of the Settlement. The attorneys' fee provision, the unknown role of the Representative Plaintiffs, and the lack of transparency throughout the settlement process all show that the settlement is a "sell-out of an otherwise strong case." *GM Trucks*, 55 F.3d at 806.

a. The Attorneys' Fee Provision

The NFL Defendants – in what is known as a "clear sailing agreement" – have agreed not to object to Class Counsel's \$112.5 million attorneys' fee award. Settlement § 21.1. The "'very existence of a clear sailing provision increases the likelihood that class counsel will have bargained away something of value'" – like compensation for all cases of CTE – "'to the class.'" *In re Bluetooth Headset Prods. Liab. Litig.*, 654 F.3d 935, 948 (9th Cir. 2011) (quoting *Weinberger v. Great N. Nekoosa Corp.*, 925 F.2d 518, 525 (1st Cir. 1991)). As a result, clear sailing agreements are "disfavored." *Id.* at 949.

It appears that Class Counsel "pursued a deal with the defendants separate from . . . the deal negotiated on behalf of the class." *GM Trucks*, 55 F.3d at 803. Although Class Counsel have stated that the "Settling Parties did not discuss the issue of attorneys' fees at any point during the mediation sessions," Dkt. No. 6073-5 at 30, those remarks are "self-serving" and may be ignored, *Bluetooth Headset*, 654 F.3d at 948 (quoting *GM Trucks*, 55 F.3d at 804). Instead, the timing of the Settling Parties' fee negotiations, which occurred even before public release of the initial settlement agreement, as well as the extraordinary sum to be paid, demonstrates the absence of arm's-length negotiations.

As if a nine-figure attorneys' fee award for conducting no discovery whatsoever were not enough, the Settlement authorizes Class Counsel to petition the Court for a 5% set aside – *drawn from each claimant's settlement award* – to "facilitate the Settlement program and related efforts of Class Counsel." Settlement § 21.1. That provision – which was not even in the initial, rejected settlement – places no limits on how Class Counsel may use the set aside (although it does require that any petition describe "how the money will be used"). *Id.* The provision gives no mechanism for providing notice to class members of Class Counsel's petition for the set aside. It also does not authorize any procedures by which class members can oppose that

petition. The set aside thus allows Class Counsel the opportunity to augment their \$112.5 million attorneys' fee at the expense of the class.

b. The Role of the Representative Plaintiffs

The role of the Representative Plaintiffs has not been disclosed. The protection of absentee class members' rights "depends in part on the extent the named plaintiffs are adequately interested to monitor the attorneys." *GM Trucks*, 55 F.3d at 784. The "specter of collusion" is present when class counsel "'prosecute an action and negotiate settlement terms without meaningful oversight by the class representative.'" *Olden v. Gardner*, 294 F. App'x 210, 219 (6th Cir. 2008) (quoting *In re Cal. Micro Devices Sec. Litig.*, 168 F.R.D. 257, 262 (N.D. Cal. 1996)). The Representative Plaintiffs have not shown such meaningful oversight here. Although the Settlement states that Representative Plaintiffs were shown and were familiar with the agreement, it says nothing about their participation in the negotiations. Settlement § 25.2. Nor did the mediator describe their role. Dkt. No. 6073-4. And media reports indicate that Co-Lead Class Counsel has "clashed with his own clients." When "class representatives provide[] no meaningful oversight of the class counsel during the settlement negotiations," the "risk of collusion weighs against the settlement." *Olden*, 294 F. App'x at 219.⁹³

c. The Settlement Negotiation Process

The class members have been left in the dark throughout the settlement process. *See* Hruby, *Show Us Some Math*, Sportsonearth.com (Jan. 20, 2014) (attached as Exhibit 70)

⁹² Fainaru & Fainaru-Wada, *Lawyers Fight Over Settlement Details*, ESPN.com (Jan. 24, 2014, 8:18 PM), http://espn.go.com/espn/otl/story/_/id/10346091/lead-negotiator-facing-strong-opposition-concussion-settlement (attached as Exhibit 69).

⁹³ Similarly, Class Counsel offer no description of the role that Sub-Class Counsel played in the negotiation. In fact, Class Counsel did not recruit Sub-Class Counsel until negotiations were *already underway* before the mediator. *See* Dkt. No. 6073-4 ¶ 7.

(describing the settlement process as "cloak[ed] [in] secrecy"). Absent class members have not, for example, had access to all negotiation documents and studies exchanged among the settling parties, Mediator, and Special Master. "Sunlight is said to be the best of disinfectants; electric light the most efficient policeman." *Buckley v. Valeo*, 424 U.S. 1, 67 (1976) (per curiam) (quoting Brandeis, *Other People's Money* 62 (Nat'l Home Library Found. ed. 1933)). That is particularly so in the class settlement context, where the court lacks the "clash of the adversaries" that ordinarily "generate[s] the information that the judge needs to decide the case." *Eubank*, 753 F.3d at 720 (rejecting class settlement); *see also Cmty. Bank*, 418 F.3d at 319 (rejecting class settlement where district court "entrusted class counsel to prepare . . . findings [of fact] in an *ex parte* closed door session" without participation of other class members). In the absence of transparency regarding the settlement negotiations, neither the Court nor the class members can be assured that Class Counsel zealously negotiated on behalf of absent class members.

F. The Likelihood of Maintaining Class Status Weighs Against Approval of the Settlement

A court must also consider "the risks of maintaining the class action through trial." *Girsh*, 521 F.2d at 157; *see also* Fed. R. Civ. P. 23(a). When the class is likely to maintain class status throughout trial, this factor weighs in favor of settlement. *GM Trucks*, 55 F.3d at 817-18.95 Here, apart from deficiencies in the adequacy of representation, the remaining class

⁹⁴ Available at http://www.patrickhruby.net/2014/01/show-us-some-math.html.

⁹⁵ Courts recognize this factor to be "more 'toothless' after" *Amchem. In re Prudential Ins.*, 148 F.3d at 321. *Amchem* held that when "[c]onfronted with a request for settlement-only class certification, a district court need not inquire whether the case, if tried, would present intractable management problems" because "the proposal" at that point in time "is that there be no trial." *Id.* (citing *Amchem Prods.*, 521 U.S. at 620). Post-*Amchem* case law thus recognizes that "the manageability inquiry in settlement-only class actions may not be significant." *Id.* at 321.

certification requirements of Rule 23(a) – numerosity, commonality, and typicality – are all satisfied. Fed. R. Civ. P. 23(a). So too is the predominance requirement. Fed. R. Civ. P. 23(b)(3). In other words, although this factor weighs in favor of *a* settlement, it weighs against *this Settlement* because of the deficiencies in the adequacy of representation.

Numerosity. Rule 23(a)(1) permits class action treatment if "the class is so numerous that joinder of all members is impracticable." Fed. R. Civ. P. 23(a)(1). The NFL Defendants themselves have conceded that this requirement is "easily met here." Dkt. No. 6073-5 at 48.

Commonality. Commonality – a threshold that "is not high," In re Sch. Asbestos Litig., 789 F.2d 996, 1010 (3d Cir. 1986) – exists if "there are questions of law or fact common to the class," Fed. R. Civ. P. 23(a)(2). Numerous issues here "arise[] from a 'common nucleus of operative facts,'" In re Orthopedic Bone Screw Prods. Liab. Litig., 176 F.R.D. 158, 174 (E.D. Pa. 1997), including: the NFL Defendants' knowledge and concealment of the health risks posed by football-related concussions, and the NFL Defendants' representations concerning those known health risks, among others.

Typicality. Typicality, also a "low threshold," *Newton v. Merrill Lynch, Pierce, Fenner & Smith, Inc., 259 F.3d 154, 183 (3d Cir. 2001), requires that "the claims or defenses of the representative parties are typical of the claims or defenses of the class." Fed. R. Civ. P. 23(a)(3). Here, for example, all class members share the same claims and suffered the same harm: neurodegenerative diseases resulting from the NFL Defendants' knowledge, concealment, and failure to warn of the severe health risks associated with repetitive blows producing subconcussive and concussive results.

Predominance. Rule 23(b)(3) class certification also requires that "the questions of law or fact common to class members predominate over any" individual questions, and that a class

action be "superior to other available methods for fairly and efficiently adjudicating the controversy." Fed. R. Civ. P. 23(b)(3). These requirements are satisfied because the crux of class members' claims concerns "the general increased risk of the class suffering medical problems," whether now or "in the future," because of Defendants' intentional or negligent misrepresentations and cover up. *Olden v. LaFarge Corp.*, 383 F.3d 495, 508-09 (6th Cir. 2004) (Rule 23(b)(3)'s predominance requirement satisfied in class action against defendant manufacturing plant where defendant's negligent conduct was the cause of class members' personal injuries and property damages, even where individual damage determinations might vary across members). 96

G. The Potential Complexity, Expense, and Likely Duration of the Litigation Weigh Against Approval of the Settlement

The complexity and likely duration of this litigation do not favor settlement. Although "[t]his factor is intended to capture 'the probable costs, in both time and money, of continued litigation,'" *GM Trucks*, 55 F.3d at 811, "all class action law suits involve complex issues, which are costly to resolve and often result in protracted proceedings," *Lachance v. Harrington*, 965 F. Supp. 630, 645 (E.D. Pa. 1997). Thus, courts focus on whether the case "involves unique issues of law or unusual fact patterns unique" to that particular species of litigation. *Id.* at 645-46. The claims presented by the retired players are hornbook tort law, presenting questions of whether the NFL assumed a duty of care, whether the NFL breached that duty, and whether that breach caused injury.

⁹⁶ Even if individual questions as to damages exist, moreover, this should not affect the predominance inquiry because "[a] district court has the discretion to split a case by certifying a class for some issues, but not others, or by certifying a class for liability alone." *Pella Corp. v. Saltzman*, 606 F.3d 391, 394 (7th Cir. 2010).

To be sure, settlement would forestall the expenses of discovery, trial preparation, and other litigation expenses. *See Cendant Corp. Litig.*, 264 F.3d at 233. But *every* settlement does that. And when a class action ends in an unfair and inadequate settlement, the litigation costs are not "saved." Rather, they are transferred to those class members whose valid claims go uncompensated because their interests were not adequately represented during the negotiation.

IV. Objectors Should Be Permitted To Object and Appear at the Fairness Hearing Even if They Later Opt Out

The "threshold requirement for exercising the opt-out right is a court's certification of a class" under Rule 23(b)(3). *Newberg on Class Actions* § 9:43 (5th ed.). "[N]o statute or rule requires notice, and an opportunity to opt out, before the certification decision is made; it is a post-certification step." *In re Bridgestone/Firestone, Inc., Tires Prods. Liab. Litig.*, 333 F.3d 763, 769 (7th Cir. 2003). This Court "conditionally certif[ied] the class for purposes of providing notice, leaving the final certification decision for the subsequent fairness hearing." Dkt. No. 6083 at 12.⁹⁷ Thus, until this Court issues a final order certifying a class action under Rule 23(b)(3), Objectors cannot be required to opt out.

Even if the Court's July 7 Order qualifies as a class certification decision that triggers the opt-out period, Objectors nevertheless have standing to object to the Settlement notwithstanding any opt-out request they may later execute. As an initial matter, someone who opts out of the

Objectors previously took the position that this Court's July 7 Order was an order granting or denying class certification under Rule 23(f). But the Third Circuit disagreed. Dkt. No. 6166. Because the Third Circuit "never accepted or adopted" that position, Objectors are not bound by that position in later litigation. *See Montrose Med. Grp. Participating Sav. Plan v. Bulger*, 243 F.3d 773, 781-82 (3d Cir. 2001). By contrast, the settling parties, having defeated Objectors' petition in the Third Circuit, cannot now urge that this Court's July 7 Order did certify a class. "'[W]here a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position." *Fleck v. KDI Sylvan Pools, Inc.*, 981 F.2d 107, 121 (3d Cir. 1992).

Settlement may, without any need for court approval, revoke their prior opt out request before the Court enters an order of final approval. Settlement § 14.2(c). Thus, until the opt-out request becomes final upon entry of a final approval order, even those who execute an opt-out request retain an interest in the terms of the Settlement agreement because they can, at their own choosing, avail themselves of the benefits of the Settlement – and might well do so if it is improved.

Additionally, a non-settling party, like a party who opts out of a class action, may still object to a class settlement agreement that causes the party legal prejudice. *See Eichenholtz v. Brennan*, 52 F.3d 478, 482-83 (3d Cir. 1995); *Newberg on Class Actions* § 13:23 (5th ed.) ("While the black letter rule is that opt-outs have no standing to object because they are not impacted, if the settlement does, for some reason, impact the rights of opt-outs, that effect could provide standing to file an objection."). This settlement would impair Objectors' legal rights in two ways, should they decide to exercise their right to opt out: It impairs their ability to fully litigate their own claims against the NFL, and it potentially deprives them of the ability to challenge a flawed class certification decision.

Further, Objectors' participation in the fairness hearing is their only opportunity to challenge a flawed class certification decision. As Objectors have noted, adequate representation was lacking here: The proposed class contains serious, fundamental intra-class conflicts that render class representation inadequate under Rule 23(a)(4). *See* pp. 20-37, *supra*. Class members' right "to opt out does not relieve the court of its duty to safeguard the interests of the class and to withhold approval from any settlement that creates conflicts among the class," *GM Trucks*, 55 F.3d at 809. In *Amchem*, for example, the Supreme Court ruled that the settlement at issue there was defective for lack of adequate representation – even though class members had the right to

opt out. 521 U.S. at 625-27. Objectors are entitled to challenge a decision certifying a conflicted class regardless of whether they opt out. But if an opt-out request prevents Objectors from objecting and participating in the fairness hearing, they face the threat of being unable to challenge that certification decision on appeal. *Cf. Devlin v. Scardelletti*, 536 U.S. 1, 6-7, 14 (2002) (holding objectors have standing and are considered a "party" for purposes of appeal).

The Settlement also hinders Objectors' ability to prosecute their own claims against the NFL because it impairs opt-out class members' ability to retain and hire experts and litigation consultants. The Settlement precludes medical professionals from serving as an expert witness or a consultant for any opt out if the professional holds a position as a BAP Provider, MAF Physician, or serves on the Appeals Advisory Panel or as an Appeals Advisory Panel Consultant. See p. 78 n.88, supra. The need for such expert testimony in a case such as this is not merely a strategic advantage or a luxury – it is a firm requirement. When "the complexities of the human body place questions as to the cause of pain or injury beyond the knowledge of the average layperson . . . the law requires that expert medical testimony be employed." Redland Soccer Club, Inc. v. Dep't of Army, 55 F.3d 827, 852 (3d Cir. 1995) (quotation marks omitted). Thus, the Settlement's effect on opt-out class members' ability to retain and hire medical experts has the effect of "strip[ping] [the opt-outs] of a legal claim or cause of action." Eichenholtz, 52 F.3d at 482.

CONCLUSION

The Court should deny final approval of the Settlement. The Court should also permit objectors to appear and be heard at the fairness hearing even if they opt out of the class before final approval.

Dated: October 6, 2014

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Appendices

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Appendix A: Background of Objectors

Objectors are seven former players who each had a significant career in the NFL. They include linemen, as well as so-called "skill position" and special teams players. The most senior began his NFL career in 1982 and the most junior retired in 2012. Three of them played on Super Bowl championship teams.

Sean Morey played for a decade with the New England Patriots, Philadelphia Eagles, Pittsburgh Steelers, Arizona Cardinals, and Barcelona Dragons, an NFL Europe team. An Ivy League stand-out at Brown University, Mr. Morey set multiple collegiate records and graduated with academic honors. In 1999, the New England Patriots selected him as a seventh round draft pick. In 2003, Mr. Morey won the Special Teams MVP award while playing with the Philadelphia Eagles. In 2004, Mr. Morey moved to the Pittsburgh Steelers, where he was captain of the special teams and earned a Super Bowl ring. He eventually moved to the Arizona Cardinals and was named to the 2008 Pro Bowl. Mr. Morey retired just before the 2010 season. While an active player, Mr. Morey co-chaired the NFLPA Mackey White Traumatic Brain Injury Committee and served as a representative in collective bargaining negotiations with the NFL. He is currently head coach of the sprint football team at Princeton University.

Alan Faneca played 13 seasons in the NFL as an offensive lineman. A star at Louisiana State University, Mr. Faneca received consensus All-American honors as a junior and was named a finalist for the prestigious Outland Trophy, which recognizes the best interior lineman in college football. Selected by the Pittsburgh Steelers in the first round of the 1998 NFL draft, Mr. Faneca was named the team's rookie of the year. A fixture on the Steelers' offensive line for ten seasons, Mr. Faneca earned a Super Bowl ring in 2006. In 2007, Steeler fans elected him to the Steelers' 75th Anniversary All Time Team. Mr. Faneca left the Steelers in 2008 for two

seasons with the New York Jets and joined the Arizona Cardinals for his final season in 2010. He was named to the Pro Bowl every year from 2001 through 2009. Since retiring from professional football, Mr. Faneca has been a tireless advocate for epilepsy research.

Ben Hamilton played ten seasons in the NFL as an offensive lineman for the Denver Broncos from 2001 until 2009, and for the Seattle Seahawks in 2010. He was a fourth-round draft pick out of the University of Minnesota. He is currently a high school math teacher at a private Christian high school in Colorado.

Robert Royal played nine seasons in the NFL from 2002 until 2010 with the Washington Redskins, Buffalo Bills, and Cleveland Browns. An All-SEC tight end at Louisiana State University, Mr. Royal averaged nearly ten yards per reception over the course of his NFL career. Mr. Royal now serves as CEO of the Robert Royal Foundation, an organization he founded to promote childhood health, fitness, and education and to combat youth violence. Mr. Royal is also involved in several private equity ventures.

Roderick "Rock" Cartwright played ten seasons in the NFL after a stellar collegiate career at Kansas State University. A fullback and kick return specialist, Mr. Cartwright played with the Washington Redskins from 2002 until 2009 and the Oakland Raiders from 2010 until 2011. In 2006, Mr. Cartwright amassed 1,541 kick-off return yards, setting a Redskins record. Since retiring from the NFL, Mr. Cartwright has actively involved himself in charity work, volunteering at a summer sports camp hosted by the Robert Royal Foundation, among others. Mr. Cartwright is also a manager with Cartwright Energy Partners LLC, an oil production development firm.

Jeff Rohrer, a second-round draft pick out of Yale University, played seven seasons in the NFL with the Dallas Cowboys from 1982 until 1989. An outside linebacker, Mr. Rohrer

received All-Ivy League honors and was the Cowboys' second- and third-leading tackler in 1986 and 1987, respectively. Since retiring from the NFL, Mr. Rohrer has worked in the film industry. He is currently a partner and executive producer at Recommended, a Los Angeles-based production company.

Sean Considine played eight seasons in the NFL as a strong safety and on special teams from 2005 until 2012. After attending the University of Iowa, Mr. Considine was drafted by the Philadelphia Eagles and played four seasons with them and then two seasons with the Jacksonville Jaguars. In 2011, he signed with the Carolina Panthers, finishing that season with the Arizona Cardinals. Mr. Considine joined the Baltimore Ravens in 2012, earning a Super Bowl ring. Since retiring from professional football, Mr. Considine has been active with numerous charities in his hometown and recently became a small business owner.

Appendix B: CTE and Its Symptoms

CTE is a distinct neurodegenerative condition caused by repetitive mild traumatic brain injury. The condition results from the build-up in the brain of mis-folded tau protein. More extensive tau build-up indicates a more advanced stage of CTE. CTE typically takes years to manifest itself. Symptoms "usually begin 8-10 years after experiencing repetitive mild traumatic brain injury." And it "spreads slowly over decades." Scientists have repeatedly documented CTE's latency period in individuals who have been exposed to repeated head trauma. CTE's symptoms include significant mood and behavioral changes as well as cognitive and motor deterioration. The symptoms worsen as the disease progresses. At present time, CTE is not readily diagnosed absent a post-mortem brain autopsy. But advances in science are making it

¹ Emery, *How to Diagnose a Battered Brain Before It's Too Late*, The Atlantic (May 8, 2012), http://www.theatlantic.com/health/archive/2012/05/how-to-diagnose-a-battered-brain-before-its-too-late/256877/ (attached as Exhibit 71); McKee *et al.*, *The Spectrum of Disease in Chronic Traumatic Encephalopathy*, 136 Brain 43, 45 (2013) ("McKee *et al.* 2013") (attached as Exhibit 5)

² Jordan, *The Clinical Spectrum of Sport-Related Traumatic Brain Injury*, 9 Nature Reviews Neurology 222, 225, 227 box 5 (2013) ("CTE is the long-term neurological consequence of repetitive mild TBI.") (attached as Exhibit 6)

³ McKee *et al.* 2013, *supra*, at 44.

⁴ *Id.* at 60.

⁵ See, e.g., Mitsis et al., Tauopathy PET and Amyloid PET in the Diagnosis of Chronic Traumatic Encephalopathies, 4 Translational Psychiatry 1, 2 (2014) (attached as Exhibit 8) ("CTE begin[s] insidiously" and "typically presents in midlife after a latency period, usually years or decades after exposure to the repetitive trauma."); Baugh et al., Chronic Traumatic Encephalopathy: Neurodegeneration Following Repetitive Concussive and Subconcussive Brain Trauma, 6 Brain Imaging & Behavior 244, 245, 246 (2012) ("Baugh et al. 2012") ("the symptoms of CTE typically do not present until years after the trauma-producing activity," and CTE has "a slow prolonged course of progression") (attached as Exhibit 17); Daneshvar et al., Long-Term Consequences: Effects on Normal Development Profile After Concussion, 22 Physical Medicine and Rehabilitation Clinics of North America 683, 691 (2011) ("Although the disease process likely starts at the time of injury, the initial signs of CTE do not typically manifest until decades later.") (attached as Exhibit 72).

possible to detect CTE earlier. The prevalence of CTE in class members cannot be overstated. The nation's largest brain bank focused on traumatic brain injury has found evidence of CTE in *76 of the 79* former players it examined.⁶

I. CTE's Symptoms

A. Mood and Behavioral Symptoms

"Mood and behavior changes are hallmark features of CTE." Mood symptoms "typically include depression, apathy, and irritability, as well as suicidality." Manic behavior, anxiety, and feelings of hopelessness have also been found in players with CTE. Behavioral symptoms are numerous. They "primarily include poor impulse control, with individuals described as having a 'short fuse' or being 'out of control." Behavioral changes also result in "[a]ggression and increased violence," as well as "[d]isinhibition."

Behavioral and mood symptoms "are often the earliest findings in CTE." So too are severe headaches. Aggressive tendencies, depression, and explosivity have also been

⁶ Breslow, 76 of 79 Deceased NFL Players Found to Have Brain Disease, PBS Frontline (Sept. 30, 2014 2:57 PM ET), http://www.pbs.org/wgbh/pages/frontline/sports/concussion-watch/76-of-79-deceased-nfl-players-found-to-have-brain-disease/ (attached as Exhibit 14).

⁷ Baugh et al. 2012, supra, at 247.

⁸ *Id.* at 246; *see also* McKee *et al.* 2013, *supra*, at 44, 52, 55-56, 58-59; Jordan, *supra*, at 226 & Box 3.

⁹ Stern et al., Clinical Presentation of Chronic Traumatic Encephalopathy, 81 Neurology 1122, 1126 tbl. 3 (2013) ("Stern et al. 2013") (attached as Exhibit 12).

¹⁰ Baugh et al., supra, at 246.

¹¹ *Id*.

¹² Jordan, *supra*, at 226; Gavett *et al.*, *Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma*, 30 Clinical Sports Medicine 179, 180 (2011) (attached as Exhibit 11) (noting "[i]n some individuals, the early manifestations of CTE affect behavior").

¹³ McKee *et al.* 2013, *supra*, at 52, 55; *see also* Baugh *et al.* 2012, *supra*, at 246 ("Early cognitive symptoms primarily include learning and memory impairment as well as executive

documented in cases of Stage I, and suicide was the cause of death in at least one documented case of Stage I CTE in a former NFL player.¹⁴ Those symptoms have also been reported in Stage II, in addition to mood instability, impulsivity, and suicidality, which was the cause of death in at least one documented case of Stage II.¹⁵ By the time CTE progresses to Stage III, depression, mood swings, and aggression are "frequently found"; other Stage III symptoms include impulsivity, and apathy.¹⁶ Suicidality is also present.¹⁷ For individuals whose CTE has progressed to Stage IV, one study found that nearly one-third experienced suicidal thoughts at some point.¹⁸

These behavioral and mood symptoms can have a profound and pernicious impact on a person's life – as well as the lives of those around them. As one study noted, CTE can lead to "worsening of cognitive and social functioning" and can "lead[] to poor money management, bankruptcy, social phobias, paranoid ideation, insomnia, poor relationships, divorce, emotional/physical abuse, and substance abuse." For example, one individual reported to have CTE – a 59-year-old physician who had suffered a traumatic brain injury while skiing – "would

dysfunction. Mood changes typically include depression, apathy, and irritability, as well as suicidality. The behavioral changes primarily include poor impulse control, with individuals described as having a 'short fuse' or being 'out of control.' Aggression and increased violence are often experienced. Disinhibition and problems with substance and other forms of abuse also occur.").

¹⁴ McKee *et al.* 2013, *supra*, at 49 tbl. 2, 52.

¹⁵ *Id.* at 50 tbl. 2, 55.

¹⁶ *Id.* at 56.

¹⁷ *Id.* at 50 tbl. 2.

¹⁸ *Id.* at 59.

¹⁹ Saulle & Greenwald, *Chronic Traumatic Encephalopathy: A Review*, Rehabilitation Research & Practice 4 (2012) (attached as Exhibit 7).

become angry and agitated, and would 'act out' in the presence of his family."²⁰ "His mood could change rapidly, and he would become withdrawn or belligerent. When in a depressed state he expressed suicidal ideation. According to the family, the patient was less emotionally available for things that had been important to him (for example, family relationships)."²¹

Another reported case of CTE involved a retired NFL football player who "became extremely reclusive and distanced himself from all personal interactions with family and friends." CTE's influence on his behavior and mood pervaded his post-NFL career:

His business activities and decisions were regarded as extraordinarily risky, ambitious, and rather irrational. In business dealings, he also exhibited sudden and unexpected fluctuations in mood and personality. At some times, he appeared hard working, ambitious, and highly driven, but at others, he exhibited sudden bouts of agitation and irritability with no clear instigator.

. . .

He became progressively incapable of mentally handling very complex rational thoughts in matters of daily living and business. He became increasingly impulsive and paranoid. His erratic behavior continued to worsen; he exhibited disinhibition, began having financial problems, and could not sustain his businesses.²³

²⁰ Mitsis, *supra*, at 3.

²¹ *Id*.

²² Omalu *et al.*, *Chronic Traumatic Encehpalopathy in a National Football League Player: Part II*, 59 Neurosurgery 1086, 1087 (2006) ("Omalu *et al.* 2006") (attached as Exhibit 57).

²³ *Id.* Such behavior is consistent with that of Dave Duerson and Junior Seau, two other prominent NFL greats diagnosed with CTE, who exhibited similarly reckless behavior and who both ultimately committed suicide in such a way as to preserve their brains for further study. *See* Stern Decl. ¶ 35; Penn, *The Violent Life and Sudden Death of Junior Seau*, GQ Magazine (Sept. 2003), http://www.gq.com/entertainment/sports/201309/junior-seau-nfl-death-concussions-braininjury (attached as Exhibit 73); Solotaroff, *Dave Duerson: The Ferocious Life and Tragic Death of a Super Bowl Star*, Men's Journal (May 2011), http://www.mensjournal.com/magazine/daveduerson-the-ferocious-life-and-tragic-death-of-a-super-bowl-star-20121002 (attached as Exhibit 74).

In 2005, he was indicted on charges of arson and wrongful business transactions; he had tried to burn down a factory he owned.²⁴

Individuals suffering from CTE are not the only ones negatively affected by these changes in behavior and mood. The "mood and behavioral changes associated with CTE are often the most concerning to family members and caregivers." As Dr. Robert Stern – one of the world's leading experts on CTE who has interviewed the family members of approximately 100 individuals who suffered from CTE – has explained, "the significant changes in mood and behavior relatively early in life . . . can lead to significant distress for the individual with CTE as well as their family, friends, and other loved ones." As Dr. Stern told Congress, "I have learned about the tremendous pain and suffering the family members experienced while their loved one's life was destroyed by the progressive destruction of the brain," by speaking with adult children of CTE victims "whose fathers had dramatic changes in personality, the development of aggressive and out-of-control behavior, and suicidal thoughts."

Indeed, the aggressive and violent behavior that often results from CTE may contribute to – though certainly does not in any way excuse – the high rates of domestic violence among current and former NFL players.²⁸ As one study found, NFL players are 55.4% more likely to be

²⁴ Omalu *et al.* 2006, *supra*, at 27.

²⁵ Baugh et al. 2012, supra, at 247.

²⁶ State of Play: Brain Injuries and Diseases of Aging: Hearing Before the S. Special Comm. on Aging, 113th Cong. 3 (2014), at 3 (written statement of Dr. Robert Stern) ("Stern Testimony") (attached as Exhibit 13), http://www.aging.senate.gov/imo/media/doc/Stern_6_25_14.pdf.

²⁷ *Id.* at 4-5.

²⁸ See Zirin, Are Head Injuries the Bridge Between the NFL Playing Field and Domestic Violence, The Nation (Sept. 21, 2014), http://www.thenation.com/blog/181695/are-head-injuries-bridge-between-nfl-playing-field-and-domestic-violence# (attached as Exhibit 75); Emison, Will NFL & NFLPA Admit Concussion Link to Domestic Violence?, The Legal Examiner (Sept. 16, 2014), http://kansascity.legalexaminer.com/?p=3871&preview=true (attached as Exhibit 76);

arrested for domestic violence relative to the national average for men ages 25 to 29.²⁹ In three cases of domestic violence committed by an NFL player, the:

similarities were stunning. In all three cases, the violence was precipitated either by migraine headaches or self-medicating – drugs or alcohol – to manage migraines. In all three cases, the survivors spoke about their NFL husbands becoming disoriented or light-sensitive, easily frustrated and quick to anger in ways that did not exist earlier in the relationship.³⁰

All are symptoms and clinical presentations of CTE. And "football players may be aware of any effects they may have on others, but are unable to change their behavior because of weaknesses in thinking flexibly and inhibition." That, in turn, might "contribute to depression observed in former athletes with CTE" because they know what they are doing is harmful but have decreased ability to control their impulses.³²

B. Cognitive and Motor Symptoms

The symptoms of CTE extend far beyond mood and behavioral disorders. CTE also affects cognitive and motor abilities. CTE's cognitive symptoms typically present as memory impairment, executive dysfunction (such as problems with planning, organization, multi-tasking, and judgment), language impairment, visuospatial difficulties, and impaired concentration and

Frankel, *Real Sports with Bryant Gumbel* (Sept. 23, 2014), http://deadline.com/2014/09/real-sports-with-bryant-gumbel-nfl-domestic-violence-head-injuries-839904/ (describing domestic violence committed by former NFL player who was ultimately diagnosed with CTE).

²⁹ Emison, *supra*.

³⁰ Zirin, *supra*.

³¹ Seichepine et al., Profile of Self-Reported Problems with Executive Functioning in College and Professional Football Players, 30 J. Neurotrauma 1299, 1302 (2013) (attached as Exhibit 77).

 $^{^{32}}$ Id.

attention.³³ Although some cognitive symptoms present during the earlier stages of the disease, dementia typically does not occur until the CTE reaches Stage III and Stage IV.³⁴

CTE also results in a panoply of movement disorders and motor presentations. These symptoms include gait disturbance, tremors, muscle weakness, and spasticity.³⁵ They also include slowed, slurred, and dysarthic speech.³⁶ "The severity of the clinical manifestation progresses through the course of the disease as the neurodegeneration increases."³⁷ These extreme symptoms are consistent with the "generalized atrophy of the brain with reduced brain weight" that occurs in advanced stages of CTE.³⁸

II. Diagnosing CTE

While a devastating, degenerative, and distinct medical condition, CTE is not readily diagnosed absent a post-mortem brain autopsy.³⁹ Scientific advances, however, are making it possible to detect CTE earlier.⁴⁰ Just a few months ago, researchers at Mt. Sinai in New York City reported a combination of tracers that bind to various brain proteins to diagnose CTE in living patients – one of whom was a former NFL player.⁴¹ And researchers in Chicago are

³³ Jordan, *supra*, at 226 box 3; Baugh *et al.* 2012, *supra*, at 246; Stern Testimony, *supra*, at 5.

³⁴ McKee *et al.* 2013, *supra*, at 56 tbl. 4, 60.

³⁵ Jordan, *supra*, at 226, box 3; Stern Testimony, *supra*, at 5; McKee *et al.* 2013, *supra*, at 59; Baugh *et al.* 2012, *supra*, at 247; Daneshvar *et al.*, *supra*, at 691.

³⁶ Jordan, *supra*, at 226 box 3; Stern Testimony, *supra*, at 5.

³⁷ Baugh et al. 2012, supra, at 246.

³⁸ *Id.* at 247.

³⁹ Jordan, *supra*, at 226.

⁴⁰ See Emery, supra (noting "pilot studies show promise for [using] diagnostic MRI and MRS scans [to diagnose CTE] as brain imaging technology improves").

⁴¹ Mitsis, *supra*, at 1-2, 7-8. Other research teams are also working to develop tracers for the tau protein that is indicative of CTE. *E.g.*, Wagner, *Can Science See Inside an NFL Player's Skull Before It's Too Late?*, Deadspin (June 21, 2012), http://regressing.deadspin.com/5920006/can-

developing a CTE screening test that relies on irregularities in vision, eye movements, and retinal/optic nerve structure as indicators of CTE.⁴² Thus, long before the Settlement concludes its 65-year term, it is likely that a large number of living class members will have received a diagnosis of CTE before they die. Even with current technology, doctors can identify likely cases of CTE based on an individual's exposure to repeated concussive and sub-concussive head impacts and symptoms – behavioral/mood, cognitive, and motor – that display during an individual's lifetime and that correlate with a post-mortem diagnosis of CTE.

science-see-inside-an-nfl-players-skull-before-its-too-late (attached as Exhibit 78); Maruyama *et al.*, *Imaging of Tau Pathology in a Tauopathy Mouse Model and in Alzheimer Patients Compared to Normal Controls*, 79 Neuron 1094 (2013) (attached as Exhibit 79); Hollmer, *Alzheimer's Diagnosis May Gain from PET Imaging of Tau Proteins*, FierceDiagnostics (Sept. 20, 2013), http://www.fiercediagnostics.com/story/alzheimers-diagnosis-may-gain-pet-imaging-tau-proteins/2013-09-20 (attached as Exhibit 80); Jagust, *Time for Tau*, 137 Brain 1570 (2014) (attached as Exhibit 81).

⁴² McGrath, *Illinois Eye Institute Project Aims to Identify CTE in the Living*, Chicago Sun-Times (June 14, 2014 4:35 PM), http://www.suntimes.com/sports/28048920-419/illinois-eye-institute-project-aims-to-identify-cte-in-the-living.html#.U6CR0fldV8E (attached as Exhibit 82).

CERTIFICATE OF SERVICE

I hereby certify that on October 6, 2014, I caused the foregoing Objection to the June 25, 2014 Class Action Settlement and supporting documents to be filed with the United States

District Court for the Eastern District of Pennsylvania via the Court's CM/ECF system, which

will provide electronic notice to all counsel of record.

/s/ Steven F. Molo

Steven F. Molo

UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated,

Plaintiffs,

V.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cv-00029-AB

DECLARATION OF ERIC R. NITZ

Eric R. Nitz declares, pursuant to 28 U.S.C. § 1746:

- 1. I am an associate at MoloLamken LLP.
- 2. Sean Morey has retained MoloLamken LLP in connection with the above-captioned matter, and I represent Mr. Morey in this matter.
- 3. Alan Faneca has retained MoloLamken LLP in connection with the above-captioned matter, and I represent Mr. Faneca in this matter.
- 4. Ben Hamilton has retained MoloLamken LLP in connection with the above-captioned matter, and I represent Mr. Hamilton in this matter.

- 5. Sean Considine has retained MoloLamken LLP in connection with the above-captioned matter, and I represent Mr. Considine in this matter.
- 6. Robert Royal has retained MoloLamken LLP in connection with the above-captioned matter, and I represent Mr. Royal in this matter.
- 7. Roderick "Rock" Cartwright has retained MoloLamken LLP in connection with the above-captioned matter, and I represent Mr. Cartwright in this matter.
- 8. Jeff Rohrer has retained MoloLamken LLP in connection with the above-captioned matter, and I represent Mr. Rohrer in this matter.
- 9. Attached as Exhibit 1 is a true and correct copy of *NFL Lawsuits for Football Concussions*, Seeger Weiss LLP, http://www.seegerweiss.com/football-concussions/#ixzz3CByVHxui, accessed on September 9, 2014.
- 10. Attached as Exhibit 2 is a true and correct copy of the Irell & Manella LLP press release, *NFL*, *Retired Players Resolve Concussion Litigation*, http://static.nfl.com/static/content/public/photo/2013/08/29/0ap2000000235504.pdf, accessed on October 1, 2014.
- 11. Attached as Exhibit 3 is a true and correct copy of Schwarz, *Concussion Committee Breaks with Predecessor*, N.Y. Times (June 1, 2010), http://www.nytimes.com/2010/06/02/sports/football/02concussion.html, accessed on October 1, 2014.
- 12. Attached as Exhibit 4 is a true and correct copy of Schwarz, *N.F.L. Acknowledges Long-Term Concussion Effects*, N.Y. Times (Dec. 20, 2009), http://www.nytimes.com/2009/12/21/sports/football/21concussions.html? r=0, accessed on October 1, 2014.
- 13. Attached as Exhibit 5 is a true and correct copy of McKee *et al.*, *The Spectrum of Disease in Chronic Traumatic Encephalopathy*, 136 Brain 43 (2013).

- 14. Attached as Exhibit 6 is a true and correct copy of Jordan, *The Clinical Spectrum of Sport-Related Traumatic Brain Injury*, 9 Nature Reviews Neurology 222 (2013).
- 15. Attached as Exhibit 7 is a true and correct copy of Saulle & Greenwald, *Chronic Traumatic Encephalopathy: A Review*, Rehabilitation Research & Practice (2012), http://www.hindawi.com/journals/rerp/2012/816069/.
- 16. Attached as Exhibit 8 is a true and correct copy of Mitsis *et al.*, *Tauopathy PET and Amyloid PET in the Diagnosis of Chronic Traumatic Encephalopathies*, 4 Translational Psychiatry 1 (2014).
- 17. Attached as Exhibit 9 is a true and correct copy of Baugh *et al.*, *Current Understanding of Chronic Traumatic Encephalopathy*, 16 Current Treatment Options in Neurology 306 (2014).
- 18. Attached as Exhibit 10 is a true and correct copy of Montenigro *et al.*, *Clinical Subtypes of Chronic Traumatic Encephalopathy*, 6 Alzheimer's Research & Therapy 68 (2014).
- 19. Attached as Exhibit 11 is a true and correct copy of Gavett *et al.*, *Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma*, 30 Clinical Sports Medicine 179 (2011).
- 20. Attached as Exhibit 12 is a true and correct copy of Stern *et al.*, *Clinical Presentation of Chronic Traumatic Encephalopathy*, 81 Neurology 1122 (2013).
- 21. Attached as Exhibit 13 is a true and correct copy of *State of Play: Brain Injuries* and Diseases of Aging: Hearing Before the S. Special Comm. on Aging, 113th Cong. (2014).
- 22. Attached as Exhibit 14 is a true and correct copy of Breslow, 76 of 79 Deceased NFL Players Found to Have Brain Disease, PBS Frontline (Sept. 30, 2014), http://www.pbs.org/

wgbh/pages/frontline/sports/concussion-watch/76-of-79-deceased-nfl-players-found-to-have-brain-disease/, accessed on October 3, 2014.

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I declare under penalty of perjury that the foregoing is true and correct.

Dated: October 6, 2014

Eric R. Nitz

EXHIBIT 1

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Up-to-Date Information on NFL Football Concussions

After years of denying the scientific evidence that links repeated football concussions with long-term brain damage, the NFL is currently in the hot seat. A flood of multi-district NFL lawsuits are finally making this powerful organization take notice.

As Plaintiffs' Co-Lead Counsel, we deeply care about this topic—and about keeping the public up-to-date on the latest findings and pursuit of justice. We encourage those of you who would like to simply stay abreast of this volatile topic or those who want helpful information for a possible lawsuit, to bookmark this page.

What's Currently Happening?

- Thousands of players who have suffered football concussions are filing NFL lawsuits.
- Christopher A. Seeger has been appointed as Co-Lead of the multidistrict litigation (MDL) effort. More

In the News

- Recent news has been flooded with terrible stories of former football players who have suffered tragic ends.
- In 1994, The National Football League created the Mild Traumatic Brain Injury Committee to investigate the effects of concussions in football.
- On December 6, 2011, Seeger Weiss reports representing 11 former NFL players suffering from football concussion-related health issues. New release
- On December 21, 2011, the NFL reported that an independent trainer would be at each NFL game to watch for potential football concussions.
 Read more

An Act of Negligence

While knowing the real truth behind concussions in football, the NFL concealed the truth to profit at the expense of the players' health. The damage caused by this fraud and negligence has caused painful and irreversible damage to many players and their families.

The NFL, which formed its own institute to study the effects of football concussions, is believed to have misled players about the harms of football concussions for their own financial gain. A culture was created where players were encouraged by coaches and franchises to play hurt and to contribute at any possible cost. Repeated football concussions have serious long-term consequences and have negatively affected the quality of life of many former players.

Link to CTE and Alzheimer's

Frequent brain trauma or multiple football concussions, at the rate of former professional football players who are filing NFL lawsuits, has shown to cause serious mental health problems. Thousands of football players, many of whom are thought to have suffered more than one hundred mild traumatic brain injuries, are dealing with horrible JA3144

Don't Suffer Alone

Are you a professional football player who has suffered from a concussion-related disease?

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Full Name	
Email	Phone

Have you experienced health problems due to a NFL concussion?



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and debilitating symptoms.

Multiple medical studies have found direct correlation between football concussions and suffering from symptoms of chronic traumatic encephalopathy, also known as CTE. CTE is believed to be the most serious and harmful disease that results from NFL and concussions. CTE is a progressive degenerative disease that causes damage to the brain tissue and the accumulation of Tau Proteins. Tau proteins aid in the onset of dementia and have been linked to the development of Alzheimer's disease.

Symptoms of CTE include:

- Dementia
- · Memory loss
- Depression
- Aggression
- · And difficulty controlling impulses

Some Players Experienced More Than 100 Mild Brain Injuries

Football concussions interfere with normal brain function and cause a variety of physical, cognitive, and emotional symptoms. The most common and immediate symptoms of a concussion are a headache, dizziness, vomiting, and temporary breakdown in motor coordination.

Confusion, disorientation, and difficulty focusing can also be NFL and concussion related side-effects as well.

When a concussion in football occurs, the force is strong enough that the cerebrospinal fluid (which protects each of our brains) cannot protect the brain from absorbing the force. A football concussion doesn't necessarily occur from direct trauma to the head, but can also result from an impulsive force like whiplash. Diagnosis of a football concussion is based on a combination of physical and neurological examinations.

Seeger Weiss LLP

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EXHIBIT 2

ALTERNATIVE DISPUTE RESOLUTION CENTER

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NFL, RETIRED PLAYERS RESOLVE CONCUSSION LITIGATION; COURT-APPOINTED MEDIATOR HAILS "HISTORIC" AGREEMENT

Thousands of Retirees and Families to Benefit

Medical Testing; Research; Compensation and Promotion of Safety All Part of Agreement

Former United States District Judge Layn Phillips, the court-appointed mediator in the consolidated concussion-related lawsuits brought by more than 4,500 retired football players against the National Football League and others, announced today that the parties had reached an agreement that would end the litigation against the NFL and NFL Properties and provide medical and other benefits, as well as compensation, to qualifying injured players or their families.

The agreement came after nearly two months of intensive negotiations under the supervision of Judge Phillips. It will be submitted for approval to United States District Judge Anita B. Brody, who is presiding over these cases in federal court in Philadelphia. Under the agreement, the NFL and NFL Properties will contribute \$765 million to provide medical benefits and injury compensation for retired NFL football players, fund medical and safety research, and cover litigation expenses. Attorneys' fees, to be approved by the district court, will be paid in addition to the settlement amount.

"This is a historic agreement, one that will make sure that former NFL players who need and deserve compensation will receive it, and that will promote safety for players at all levels of football," said Judge Phillips. "Rather than litigate literally thousands of complex individual claims over many years, the parties have reached an agreement that, if approved, will provide relief and support where it is needed at a time when it is most needed. I am deeply grateful to Judge Brody for appointing me as mediator and offering me the opportunity to work on such an important and interesting matter."

"This agreement lets us help those who need it most and continue our work to make the game safer for current and future players. Commissioner Goodell and every owner gave the legal team the same direction: do the right thing for the game and for the men who played it," said NFL Executive Vice President Jeffrey Pash. "We thought it was critical to

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Alternative Dispute Resolution Center

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get more help to players and families who deserve it rather than spend many years and millions of dollars on litigation. This is an important step that builds on the significant changes we've made in recent years to make the game safer, and we will continue our work to better the long-term health and well-being of NFL players."

"This is an extraordinary agreement that will provide immediate care and support to retired players and their families," said lead plaintiffs' attorney Christopher Seeger of Seeger Weiss LLP. "This agreement will get help quickly to the men who suffered neurological injuries. It will do so faster and at far less cost, both financially and emotionally, than could have ever been accomplished by continuing to litigate."

"The benefits in this agreement will make a difference not only for me and my family, but also for thousands of my football brothers who either need help today or may need help someday in the future," said Kevin Turner, a former running back for the Philadelphia Eagles and New England Patriots. Turner, who has been diagnosed with ALS, will serve as the lead plaintiff for one group of retired players. "I am grateful that the NFL is making a commitment to the men who made the game what it is today."

Once final documentation is completed, the settlement will be filed with Judge Brody, who will then schedule a hearing to consider whether to grant preliminary approval to the agreement. If the settlement receives preliminary approval, Judge Brody will direct the parties to distribute notice to the retired players. After giving retired players an opportunity to file objections to the settlement, Judge Brody will hold a hearing to consider whether to grant final approval. Judge Brody is expected to issue the precise schedule within a few weeks.

"Approval of the settlement will require Judge Brody to determine that it is fair, reasonable, and adequate in light of the claims and defenses, and the expense, uncertainty and time inherent in litigating the claims, particularly given the benefits provided by the agreement," said Judge Phillips. "There is no question that this settlement will provide benefits much sooner, and at much less cost, for many more retirees, than would have been achieved through extended litigation. For these and other reasons, I will strongly endorse this settlement in my report to Judge Brody."

A summary of the key terms of the agreement is attached.

JA3148

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Principal Terms of NFL Litigation Settlement

<u>Class Settlement</u> – The settlement will include all players who have retired as of the date on which the Court grants preliminary approval to the settlement agreement, their authorized representatives, or family members (in the case of a former player who is deceased).

No Admissions of Liability or Weakness of Claims – The settlement does not represent, and cannot be considered, an admission by the NFL of liability, or an admission that plaintiffs' injuries were caused by football. Nor is it an acknowledgement by the plaintiffs of any deficiency in their case. Instead, it represents a decision by both sides to compromise their claims and defenses, and to devote their resources to benefit retired players and their families, rather than litigate these cases.

<u>Payments</u> – The NFL and NFL Properties will make payments in connection with the settlement as follows:

- (A) Baseline medical exams, the cost of which will be capped at \$75 million;
- (B) A separate fund of \$675 million to compensate former players who have suffered cognitive injury or their families;
- (C) A separate research and education fund of \$10 million;
- (D) The costs of notice to the members of the class, which will not exceed \$4 million;
- (E) \$2 million, representing one-half of the compensation of the Settlement Administrator for a period of 20 years; and
- (F) Legal fees and litigation expenses to the plaintiffs' counsel, which amounts will be set by the District Court.

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<u>Timing of Payments</u> – If the agreement receives preliminary approval from the District Court, the NFL will pay the costs of preparing and distributing notice to the class members (up to \$4 million). If the settlement receives final approval, and any appeals have been concluded, the NFL will pay approximately 50 percent of the settlement amount over three years, and the balance over the next 17 years.

<u>Baseline Medical Examinations</u> – Eligible retired players may receive a Baseline Medical Assessment, the results of which will be used to establish a qualifying diagnosis, either now or at a point in the future. The baseline examination program will operate for a period of 10 years. After 10 years, any funds allocated for this program that have not been spent will be added to the fund for payment of monetary awards.

<u>Injury Compensation Fund</u> – The fund of at least \$675 million will be available to pay monetary awards to retired players who present medical evidence of severe cognitive impairment, dementia, Alzheimer's, ALS, or to their families. The precise amount of compensation will be based upon the specific diagnosis, as well as other factors including age, number of seasons played in the NFL, and other relevant medical conditions. These determinations will be made by independent doctors working with settlement administrators appointed by the District Court.

If a retired player's condition worsens over time, he may apply for a supplemental payment.

In the event the Injury Compensation Fund ultimately is deemed insufficient to pay all approved claims, the Settlement Administrator will make a recommendation to the Court that the NFL make an additional, one-time contribution to the Injury Compensation Fund up to a maximum amount of \$37.5 million.

<u>Research and Education Fund</u> – The NFL will allocate \$10 million toward medical, safety, and injury-prevention research, and toward educating retired players on NFL benefits programs. A portion of this fund will be used to support joint efforts by the NFL and retired NFL players to promote education and safety initiatives in youth football.

<u>Other Benefits</u> – No retired player will forfeit or become ineligible for any other benefits provided by the current Collective Bargaining Agreement between the NFL and the NFL Players Association.

<u>Schedule for Further Activity</u> – The parties will prepare and file complete agreements with Judge Brody in Philadelphia, who will then schedule a hearing to consider whether to grant preliminary approval to the settlement. Assuming preliminary approval is granted, the Judge will direct that notice be given to the retired players and will schedule a hearing to consider whether to grant final approval to the settlement.

JA3150

ALTERNATIVE DISPUTE RESOLUTION CENTER

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Q & A with Judge Layn Phillips on NFL Litigation Settlement

Who will receive the money and how?

Retired players will have the opportunity to participate in baseline medical exams. Players with demonstrated cognitive injury, now or in the future, will be able to obtain a monetary award. The decisions regarding who qualifies and the amount of the award will be made by independent doctors and fund administrators agreed upon by the parties, and the federal court in Philadelphia will retain ultimate oversight.

How will the medical monitoring work?

A nationwide network of health care providers will be available to give the baseline exams to retired players. The goal will be to make the exam sites convenient so that as many retirees as possible can take advantage of the potential medical benefits.

Is this an acknowledgement by the NFL that it hid information on long-term effects?

No. An agreement doesn't imply anything about either side's position. It doesn't mean that the NFL hid information or did what the plaintiffs claimed in their complaint. It does not mean that the plaintiffs' injuries were caused by football or that the plaintiffs would have been able to prove that their injuries were caused by football. On the other hand, it doesn't mean that the plaintiffs wouldn't have been able to prove their case. The settlement means that the parties reached an agreement to put litigation behind them, get help to retired players who need it, and work proactively to support research and make the game safer. These are goals everyone can share.

What would be the process without a settlement?

Absent a certified litigation class or some creative form of consolidation, every case would have to be addressed individually. Doing so would be complicated, time consuming, expensive, and the outcome for both sides would be highly uncertain.

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Casea18-2012mdD003113ehB 003111331658201-Pagee1820/06Date Filed:108/09/2019

Alternative Dispute Resolution Center

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How were you able to get the parties to settle something that seemed so contentious?

To their credit, both sides recognized that it would be far more productive to get out of court and do something good for retired players with medical needs and focus on the future of the game and making it safer. I would characterize it as a 'win-win.' The alternative was for the two sides to spend the next 10 years and millions of dollars on litigation, which would have been great for lawyers, expert witnesses, trial consultants and others. But it would not do much for retired players and their families who are in need. This resolution allows the sides to join together, do something constructive, and build a better game for the future. Both sides faced major risks and uncertainties that made a class settlement far and away the best path for resolving these issues.

Will this prevent other lawsuits of this nature from being filed?

For a variety of reasons, the underlying theory of this lawsuit about what took place in the past would be difficult to replicate in the future. Everyone now has a much deeper and more substantial understanding about concussions, and how to prevent and manage them, than they did 20 or even 10 years ago, and the information conveyed to players reflects that greater understanding. In addition, the labor law defenses asserted by the NFL would represent a very substantial barrier to asserting these kinds of claims going forward. The combination of advances in medical research, improved equipment, rules changes, greater understanding of concussion management, and enhanced benefits should, and hopefully will, prevent similar lawsuits in the future.

What should parents of kids who play football take from this settlement?

Parents should know that the NFL and the plaintiffs are committed to doing what's right for the game and making it safer at all levels. The proposed settlement includes funds for medical research and education to support those goals.

²⁸⁴⁸⁰⁴¹ JA3152

EXHIBIT 3

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June 1, 2010

Concussion Committee Breaks With Predecessor

By ALAN SCHWARZ

WASHINGTON — They accused a fellow doctor of minimizing solid evidence of the dangers of football concussions. They concurred that data collected by the N.F.L.'s former brain-injury leadership was "infected," said that their committee should be assembled anew, and formally requested that the group's former chairman, Dr. Elliot Pellman, not speak at a conference Wednesday.

For the first time these remarks came not from outside critics of N.F.L. research but from those now in charge of it — Dr. H. Hunt Batjer and Dr. Richard G. Ellenbogen, prominent neurosurgeons who became co-chairmen of a new league committee in March. One week after two members of Congress accused the doctors of sounding too much like their predecessors, and on the eve of a league-sponsored symposium in Washington held by Johns Hopkins Medicine, Batjer and Ellenbogen made clear they planned to chart a new course.

The two doctors criticized Johns Hopkins's promotional brochure for Wednesday's conference — which was open only to N.F.L. medical personnel, other doctors and members of the United States Department of Defense — for playing down existing evidence of brain damage in retired football players.

The opening paragraph described the disease chronic traumatic encephalopathy as "now being reported in football players, although with unknown frequency." It added that these and related matters had been reported by the news media "with considerable hype around assertions of long-term harm to players from head injuries."

Batjer and Ellenbogen said that the frequency of reports of C.T.E. in players is not unknown — a Boston University research group has diagnosed it in all 12 former college and N.F.L. players of various ages it had tested for the condition.

"They aren't assertions or hype — they are facts," said Ellenbogen, the chief of neurological surgery at Harborview Medical Center in Seattle, who has been instrumental in drafting legislation to protect young athletes from head injuries.

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He added: "Doctors were relatively ineffectual for 25 years on this issue. Then it's on the front page and everything focuses like a laser beam and things begin to change from baby steps to giant steps forward protecting kids. From a doctor-patient perspective, it's been the single best thing that has happened to this subject."

Dr. Constantine G. Lyketsos, a professor of psychiatry and behavioral sciences at Johns Hopkins who is directing Wednesday's conference, said in a telephone interview that he wrote the brochure and that the N.F.L. had no role with the event, other than providing financing. He defended his choice of words.

"We know of 12 cases" of C.T.E., Lyketsos said. "We don't know how many don't have it."

Regarding news media coverage of the harm caused by repeated concussions in football players, Lyketsos said: "There is a concern that I have that the possibility of serious long-term consequences are being overemphasized without clear evidence. It could turn out correct. It could turn out incorrect. We don't know."

He added: "I worry that it might be a disservice. That's a possibility."

The league spokesman Greg Aiello declined to comment on Lyketsos's statements, other than saying that the league has given \$1 million to the Boston University group to support its research.

The former leaders of the N.F.L. concussion committee generally agreed with Lyketsos, an attitude that ultimately came to the attention of Congress and led to several hearings on the subject of sports concussions in athletes of all ages. Batjer and Ellenbogen had a shaky debut before some frustrated members of the House Judiciary Committee during a forum in New York on May 24, but in the following days they made sure they would no longer resemble their predecessors.

The doctors said the old committee's ongoing studies on helmets and retired players' cognitive decline — whose structure and data were strongly criticized by outside experts — would not be used in any way moving forward. They said they were influenced by a comment made to them last Monday by Representative Anthony D. Weiner, Democrat of New York: "You have years of an infected system here that your job is to some degree to mop up."

"The word 'infected' hit me right between the eyes," said Ellenbogen. He and Batjer became cochairmen of the N.F.L. committee in March.

Batjer added: "We all had issues with some of the methodologies described, the inherent conflict of interest that was there in many areas, that was not acceptable by any modern

10/1/2014 standards or not acceptable to us. I wouldn't put up with that, our universities wouldn't put up with that, and we don't want our professional reputations damaged by conflicts that were put upon us."

Batjer said that he and Ellenbogen had begun reconstituting their committee from scratch. He said that six members had been selected so far, none of them holdovers from the prior regime.

The doctors so wanted to distance themselves from the past that on Monday they requested that Pellman, who was scheduled to deliver some opening remarks at the Johns Hopkins symposium, be removed from the program. Pellman was the chairman of the N.F.L. concussion committee from 1994 to 2007 and stayed on it until he resigned in March. He remains the league's medical director and helped with the conference's logistics.

On Tuesday, an e-mail message was distributed to conference organizers saying that Pellman would not attend the conference for family-related reasons.

"Neither Rich nor I thought he should appear to represent the N.F.L. in what would look like a leadership role," Batjer said. "It's not about Elliot. It's about a complete severance from all prior relationships from that committee."

Aiello, the league spokesman, indicated that the N.F.L. would not scrutinize or attempt to influence the committee's leadership.

"Drs. Ellenbogen and Batjer have full authority to make decisions regarding the work of the Head, Neck and Spine Committee, including organization, membership, status of current and new research, and the like," Aiello said. "We fully support them and will continue to do so."

EXHIBIT 4

The New York Times

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December 21, 2009

N.F.L. Acknowledges Long-Term Concussion Effects

By ALAN SCHWARZ

After weeks of transforming its approach to concussions and its research into their long-term effects among players, the <u>N.F.L.</u> not only announced Sunday that it would support research by its most vocal critics but also conceded publicly for the first time that concussions can have lasting consequences.

"It's quite obvious from the medical research that's been done that concussions can lead to long-term problems," the league spokesman Greg Aiello said in a telephone interview. He was discussing how the league could donate \$1 million or more to the Center for the Study of Traumatic Encephalopathy at <u>Boston University</u>, whose discoveries of brain damage commonly associated with boxers in the brains of deceased football players were regularly discredited by the N.F.L.

Told that his statement was the first time any league official had publicly acknowledged any long-term effects of concussions, and that it contradicted past statements made by the league, its doctors and literature currently given to players, Aiello said: "We all share the same interest. That's as much as I'm going to say."

Since an Oct. 28 <u>hearing before the House Judiciary Committee</u>, when the league's approach to science was compared to that of the tobacco industry, the N.F.L. has accepted the resignations of the co-chairmen of its concussion committee and overhauled its policies toward concussion management. Players now must be cleared by brain-injury experts unaffiliated with the team, and cannot return to a game or practice in which they have shown any significant sign of concussion.

The second rule has since been recommended by an <u>N.C.A.A.</u> committee as standard policy for athletes in all sports, and will be considered by several state legislatures that have bills governing high school athletics before them.

The recent changes by the N.F.L. had amounted to tacit acknowledgments that it was no longer able to defend a position that conflicted with nearly all scientific understanding of head trauma.

Until recently, the league and its committee on concussions had consistently minimized evidence testifying to the risks of repeated brain trauma in N.F.L. players — from researchers like those at Boston University, to phone surveys the league itself commissioned, to demographic analysis of players known to have early-onset dementia. While discrediting such evidence, a pamphlet on concussions currently given to players states, "Research is currently underway to determine if there are any long-term effects of concussion in N.F.L. athletes."

That research study, conducted by the N.F.L.'s committee on concussions, was recently suspended amid

10/1/2014 Casea**18-2012**md**Docy/16-hb-008148316580Pregict 139/06Date Pilgd**: **108/09/2019** strong criticism of its design and execution by outside experts, players and members of Congress.

"Mr. Aiello's statement is long overdue — it's a clear sign of how the culture of football has changed in recent months," Dr. Robert Stern, a co-director of the Boston University center and its Alzheimer's Disease Clinical and Research Program, said in a telephone interview.

"There is no doubt that repetitive blows to the head result in long-term problems in the brain, including progressive dementia. With the N.F.L. taking these recent actions, we are finally at a point to move forward in our research and ultimately solve this important problem — for professional athletes and collegiate and youth players."

Aiello said that the amount of the league's donation to the center had yet to be determined with Boston University officials. Dr. Robert Cantu, a co-director of the center with Stern, met with N.F.L. Commissioner Roger Goodell and the league lawyer Jeff Pash in October to discuss nonfinancial support for the center.

"No money was ever requested when I met with them, and I went into considerable detail on why we couldn't accept any money without consideration of conflicts of interest," said Cantu, the director of the Neurological Sports Injury Center at <u>Brigham and Women's Hospital</u> in Boston. "We can't receive any money until you know what the strings are and the strings aren't. I'm not saying it couldn't happen, but it has not been broached."

The Boston University group's work centers on receiving commitments from current and former athletes in various sports to donate their brains for examination after their deaths. (The disease primarily found in retired football players' brain tissue, chronic traumatic encephalopathy, can be diagnosed only through special staining techniques.) More than 110 athletes have registered to donate in little over a year — about 50 of them current and ex-N.F.L. players.

Discussing his participation in the program last year, Ted Johnson, a former <u>New England Patriots</u> linebacker who sustained multiple concussions that have caused significant memory and emotional problems through his 30s, indicated his frustration at the league's stance on the matter.

"I shouldn't have to prove to anybody that there's something wrong with me," he said. "I'm not being vindictive. I'm not trying to reach up from the grave and get the N.F.L. But any doctor who doesn't connect concussions with long-term effects should be ashamed of themselves."

Aiello said that regardless of any financial support, the league would encourage current and former players to donate their brains to the Boston University research. He added that the roughly 85 retired players and families receiving aid from the 88 Plan — a fund jointly administered by the league and the union to help pay the costs of retirees with dementia — would be singled out to participate. The players union has said it supports the program as well.

The work of the Boston University group has already provided some of the most compelling evidence of football's long-term effects on the brain. All 11 retired players examined for chronic traumatic encephalopathy — an exceedingly rare disorder caused by concussive and subconcussive blows to the head — have been found to have the disease, which is associated with early-onset dementia, emotional

10/1/2014 Caseate-20122mdDocardehe 0081483465800 Preger 1909/06/Date Fried: 108/09/2019 disturbances and drug abuse.

Studies at the <u>University of North Carolina</u> and the <u>University of Michigan</u> have found heightened rates of dementia and other cognitive decline, results corroborated by a New York Times demographic analysis of members of the league's 88 Plan.

After every finding, the league and its committee doctors have faulted the methods of the studies, and suggested that other causes were responsible and that the question remained open. When the league-sponsored Michigan study reported this September that retirees were reporting rates of Alzheimer's and other memory-related diseases at five times or more the national rate, Aiello said, "There are thousands of retired players who do not have memory problems," and, "Memory disorders affect many people who never played football or other sports."

Asked about those remarks Sunday, Aiello said: "We didn't say it doesn't deserve further study and attention, which is what we're trying to do. The only statement we're making is that we're doing this."

Stern said that the Boston University group had raised \$450,000 in grant support, and that he was preparing a proposal to the <u>National Institutes of Health</u>.

"This type of research is extremely expensive," Stern said. "And time is very much of the essence."

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EXHIBIT 5



The spectrum of disease in chronic traumatic encephalopathy

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Chronic traumatic encephalopathy is a progressive tauopathy that occurs as a consequence of repetitive mild traumatic brain injury. We analysed post-mortem brains obtained from a cohort of 85 subjects with histories of repetitive mild traumatic brain injury and found evidence of chronic traumatic encephalopathy in 68 subjects: all males, ranging in age from 17 to 98 years (mean 59.5 years), including 64 athletes, 21 military veterans (86% of whom were also athletes) and one individual who engaged in self-injurious head banging behaviour. Eighteen age- and gender-matched individuals without a history of repetitive mild traumatic brain injury served as control subjects. In chronic traumatic encephalopathy, the spectrum of hyperphosphorylated tau pathology ranged in severity from focal perivascular epicentres of neurofibrillary tangles in the frontal neocortex to severe tauopathy affecting widespread brain regions, including the medial temporal lobe, thereby allowing a progressive staging of pathology from stages I-IV. Multifocal axonal varicosities and axonal loss were found in deep cortex and subcortical white

^{*}These authors contributed equally to this work.

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matter at all stages of chronic traumatic encephalopathy. TAR DNA-binding protein 43 immunoreactive inclusions and neurites were also found in 85% of cases, ranging from focal pathology in stages I-III to widespread inclusions and neurites in stage IV. Symptoms in stage I chronic traumatic encephalopathy included headache and loss of attention and concentration. Additional symptoms in stage II included depression, explosivity and short-term memory loss. In stage III, executive dysfunction and cognitive impairment were found, and in stage IV, dementia, word-finding difficulty and aggression were characteristic. Data on athletic exposure were available for 34 American football players; the stage of chronic traumatic encephalopathy correlated with increased duration of football play, survival after football and age at death. Chronic traumatic encephalopathy was the sole diagnosis in 43 cases (63%); eight were also diagnosed with motor neuron disease (12%), seven with Alzheimer's disease (11%), 11 with Lewy body disease (16%) and four with frontotemporal lobar degeneration (6%). There is an ordered and predictable progression of hyperphosphorylated tau abnormalities through the nervous system in chronic traumatic encephalopathy that occurs in conjunction with widespread axonal disruption and loss. The frequent association of chronic traumatic encephalopathy with other neurodegenerative disorders suggests that repetitive brain trauma and hyperphosphorylated tau protein deposition promote the accumulation of other abnormally aggregated proteins including TAR DNA-binding protein 43, amyloid beta protein and alpha-synuclein.

Keywords: axonal injury; brain trauma; frontotemporal lobar degeneration; neurodegenerative disorders; traumatic brain injury **Abbreviations:** CTE = chronic traumatic encephalopathy; FTLD = frontotemporal lobar degeneration; MND = motor neuron disease

Introduction

Repetitive mild traumatic brain injury can trigger the development of chronic traumatic encephalopathy (CTE), a progressive neurodegeneration characterized by the widespread deposition of hyperphosphorylated tau (p-tau) as neurofibrillary tangles (Corsellis and Brierley, 1959; Corsellis et al., 1973, Hof et al., 1991; Geddes et al., 1999; Omalu et al., 2005, 2006, 2010; McKee et al., 2009, 2010; Gavett et al., 2010, 2011; Daneshvar et al., 2011a, b; Costanza et al., 2011; Stern et al., 2011; Goldstein et al., 2012; Saing et al., 2012). CTE was originally reported in 1928 by Harrison Martland, a New Jersey pathologist, who described the clinical aspects of a progressive neurological deterioration ('punch drunk') that occurred after repetitive brain trauma in boxers (Martland, 1928). Although originally termed 'dementia pugilistica' (Millspaugh, 1937), the recognition that activities other than boxing were associated with its development lead to the preferred use of terms such as progressive traumatic encephalopathy and later, CTE (Critchley, 1949; 1957).

CTE is clinically associated with symptoms of irritability, impulsivity, aggression, depression, short-term memory loss and heightened suicidality that usually begin 8–10 years after experiencing repetitive mild traumatic brain injury (McKee et al., 2009). With advancing disease, more severe neurological changes develop that include dementia, gait and speech abnormalities and parkinsonism. In late stages, CTE may be clinically mistaken for Alzheimer's disease or frontotemporal dementia (Gavett et al., 2010, 2011). A subset of cases with CTE is associated with motor neuron disease (MND) (McKee et al., 2010).

The neuropathological changes of CTE are distinctive and easily distinguished from other tauopathies, including Alzheimer's disease. The neuropathological features of CTE include generalized atrophy of the cerebral cortex, medial temporal lobe, diencephalon and mammillary bodies with enlarged ventricles; cavum septum pellucidum, often with fenestrations; extensive

p-tau-immunoreactive neurofibrillary tangles and astrocytic tangles in the frontal and temporal cortices, particularly around small cerebral vessels and at the depths of cerebral sulci; extensive p-tau-immunoreactive neurofibrillary tangles in limbic regions, diencephalon and brainstem nuclei; extensive degeneration of axons and white matter fibre bundles; TAR DNA-binding protein 43 (TDP-43) immunoreactive intraneuronal and intraglial inclusions and neurites in most cases and a relative absence of amyloid-β peptide deposits (Corsellis and Brierley, 1959; Corsellis *et al.*, 1973; Hof *et al.*, 1991; Geddes *et al.*, 1999; Omalu *et al.*, 2005, 2006, 2010; McKee *et al.*, 2009, 2010; Gavett *et al.*, 2010, 2011; Daneshvar *et al.*, 2011a, b; Costanza *et al.*, 2011; Stern *et al.*, 2011; Goldstein *et al.*, 2012; Saing *et al.*, 2012).

In 2008, the Center for the Study of Traumatic Encephalopathy (CSTE) at Boston University School of Medicine established the CSTE brain bank at the Bedford VA Hospital to analyse the brain and spinal cords after death of athletes, military veterans and civilians who experienced repetitive mild traumatic brain injury. Through this effort, we comprehensively analysed the brain and spinal cord of 85 donors for evidence of CTE, as well as for all other neurodegenerative diseases, including Alzheimer's disease, frontotemporal lobar degeneration (FTLD), Parkinson's disease, Lewy body disease and multiple system atrophy. We report the spectrum of CTE and neurodegenerative pathology found in the brain and spinal cord of these donors, compare the pathological findings with 18 cognitively normal age- and gender-matched control subjects without known history of mild traumatic brain injury, and correlate the clinical findings to the neuroanatomical regions of p-tau pathology. Although a brain donation study and autopsy directed case series will never establish the incidence or prevalence of a disorder such as CTE owing to ascertainment biases, systematic clinicopathological analysis allows insight into the spectrum of clinical and neuropathological alterations associated with the disorder and lays the foundation for future prospective longitudinal studies.

Materials and methods

Subjects

A total of 85 brains from former athletes, military veterans or civilians with a history of repetitive mild traumatic brain injury were comprehensively evaluated. Eighteen additional brains from cognitively intact individuals without history of mild traumatic brain injury were obtained from the Boston University Alzheimer's Disease Center Brain Bank that included some subjects from the Framingham Heart Study. Next of kin provided written consent for participation and brain donation. Institutional review board approval for brain donation was obtained through the Boston University Alzheimer's Disease Center, CSTE and the Bedford VA Hospital. Institutional review board approval for post-mortem clinical record review, interviews with family members and neuropathological evaluation was obtained through Boston University School of Medicine.

Clinical assessment

Concussion and mild traumatic brain injury history, history of cognitive and behavioural changes and clinical status leading up to death were determined through post-mortem interviews with next of kin performed by a neuropsychologist (R.A.S.) who was blind to the results of the neuropathological examination at the time of interview. Informants were interviewed before receiving the results of the neuropathological examination. The interview was semi-structured and conducted by telephone. Areas queried included demographics, athletic history, military service, concussion and brain trauma history, medical history (including neurological, psychiatric and substance use), family history, social/occupational history, and reported/observed changes in mood, behaviour, motor functions, cognition and activities of daily living. To semi-quantify cognitive, mood and functional changes, modifications of standard measures/interviews were administered to the informant to assess their perception of the subject in the months or years before death (Pfeffer et al., 1982; McNair et al., 1984; Brown and Schinka, 2005; Galvin et al., 2005). Medical record review was also performed (R.A.S. and A.C.M.).

In analysis of the clinical symptoms associated with CTE, case selection was restricted to those cases with post-mortem semi-structured family interviews and pathological diagnosis of CTE or CTE plus MND (CTE-MND), without other co-morbidities.

Duration of exposure to American football and position played

To examine the relationship between exposure and stage of CTE, analyses were performed on the subset of athletes who played American football. Only football played at the high school level or higher was considered for these analyses. Of the 85 brain donors, 58 played American football as their primary sport. Of those, 16 subjects were excluded owing to comorbid disease (Alzheimer's disease, Parkinson's disease, Lewy body disease, FTLD and multiple system atrophy), and seven were excluded owing to incomplete athletic information. Football players were also grouped by primary position played: offensive and defensive linemen, quarterbacks, wide receivers, all other offensive backs, defensive linebackers and defensive backs.

Neuropathological examination

The neuropathological processing followed the procedures previously established for the Boston University Alzheimer's Disease Center Brain Bank (Vonsattel et al., 1995). Paraffin-embedded sections were stained with Luxol fast blue, haematoxylin and eosin, Bielschowsky's silver, AT8, alpha-synuclein, amyloid-ß, TDP-43, phosphorylated TDP-43 (pTDP-43), SMI-31 and SMI-34 using methods described previously (McKee et al., 2009). In addition, multiple large coronal slabs of the cerebral hemispheres were cut at 50 µm on a sledge microtome and stained as free-floating sections using AT8, amyloid-ß, TDP-43, pTDP-43, CP13 and PHF-1 (McKee et al., 2009, 2010) (Supplementary Table 1). Neuropathological diagnoses were made without any knowledge of the subjects' clinical histories (A.C.M.) and confirmed by two other neuropathologists (T.D.S. and V.E.A.).

Neuropathological diagnoses

Definition of chronic traumatic encephalopathy

Based on our previous studies and review of the literature on CTE (Corsellis et al., 1973; Hof et al., 1991; Geddes et al., 1999; Omalu et al., 2005, 2006, 2010; McKee et al., 2009, 2010; Goldstein et al., 2012; Saing et al., 2012), the diagnosis of CTE was defined by the presence of the following criteria (Table 1 and Figs. 1 and 2): (i) perivascular foci of p-tau immunoreactive astrocytic tangles and neurofibrillary tangles; (ii) irregular cortical distribution of p-tau immunoreactive neurofibrillary tangles and astrocytic tangles with a predilection for the depth of cerebral sulci; (iii) clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia and brainstem; and (iv) neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers.

Definition of chronic traumatic encephalopathy-motor neuron disease

The diagnosis of CTE-MND required a clinical diagnosis of definite amyotrophic lateral sclerosis using the revised El Escorial criteria for the diagnosis of amyotrophic lateral sclerosis (Brook et al., 1994, 2000), and the pathological diagnosis of CTE, as defined above, in addition to the following criteria (McKee et al., 2010): (i) degeneration of lateral and ventral corticospinal tracts of the spinal cord; (ii) marked loss of anterior horn cells from cervical, thoracic and lumbar spinal cord with gliosis; and (iii) TDP-43 or pTDP-43 positive neuronal, glial, neuritic or intranuclear inclusions in anterior horn cells and white matter tracts of the spinal cord.

Criteria for Alzheimer's disease

The criteria for Alzheimer's disease were based on the presence of amyloid-ß neuritic plaques and p-tau neurofibrillary tangles according to the NIA-Reagan criteria for intermediate and high likelihood Alzheimer's disease and the recent NIA Alzheimer Association's guidelines (Newell et al., 1999; Montine et al., 2012). The NIA-Reagan criteria take into account both the Braak and Braak staging of neurofibrillary tangles (Braak and Braak, 1991, 1993, 1994) and the overall density of neuritic plaques based on CERAD criteria (Mirra et al., 1991). The nature, pattern and distribution of p-tau neurofibrillary degeneration in CTE are distinctive from Alzheimer's disease (Table 1 and Fig. 1; McKee et al., 2011).

Criteria for Parkinson's disease and Lewy body disease

The diagnosis of Parkinson's disease or Lewy body disease was based on the presence and distribution of alpha-synuclein-positive Lewy **46** Brain 2013: 136; 43–64

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Table 1 Distinctions in hyperphosphorylated tau pathology between Alzheimer's disease and CTE

Pathological features	Alzheimer's disease	CTE
Tau protein		
Six isoforms	All six isoforms present	All six isoforms present ^a
3 or 4 repeat tau	3 repeat and 4 repeat tau present	3 repeat and 4 repeat tau present
Cell origin		
Neuronal	NFTs and pre-tangles	NFTs and pre-tangles
Astrocytic	Not present ^b	Prominent astrocytic tangles
Neuronal domain		
Cell body	Prominent	Prominent
Dendrite	Prominent	Prominent
Axon	Sparse	Prominent
Cell Pattern		
Perivascular	Not present	Prominent NFTs and astrocytic tangles
Foci at depths of cerebral sulci	Not present	Prominent NFTs and astrocytic tangles
Irregular, patchy cortical distribution	Not present	Prominent
Cortical laminae	NFTs predominantly in laminae III and V	NFTs predominantly in laminae II-III
Subpial astrocytic tangles	Not present	Prominent
Periventricular astrocytic tangles	Not present	Present
Distribution		
Mild pathology	Braak stages I–III:	CTE stages I–II:
	NFTs in entorhinal cortex, amygdala and hippocampus	NFTs in focal epicentres in cerebral cortex, usually frontal lobe
Advanced pathology	Braak stages IV-VI:	CTE stages III–IV:
	High density of NFTs in widespread cortical areas and medial temporal lobe, uniform distribution	High density of NFTs in widespread cortical areas and medial temporal lobe, patchy irregular distribution
	Low densities of NFTs in basal ganglia and brainstem; none in mammillary bodies. White matter tracts relatively uninvolved.	High densities of NFTs in thalamus, hypothalamus, mammillary bodies, brainstem. Moderate densities of NFTs in basal ganglia, especially nucleus accumbens. Prominent p-tau pathology in white matter tracts.

a Schmidt et al., 2001.

b Low densities of 4R immunoreactive 'thorn-shaped astrocytes' are found in the temporal lobe of some older subjects and older subjects with Alzheimer's disease (Lace et al., 2012; López-González et al., 2012).

NFT = neurofibrillary tangles.

bodies and was considered brainstem-predominant (Parkinson's disease), limbic or transitional Lewy body disease, and neocortical or diffuse Lewy body disease as defined by McKeith criteria (McKeith *et al.*, 1996) and Braak staging (Del Tredici *et al.*, 2002; Braak and Del Tredici, 2008).

Criteria for frontotemporal lobar degeneration

Neuropathological diagnosis of FTLD was based on predominant involvement of the frontal and temporal lobes and characteristic immunohistochemistry for p-tau, TDP-43 and p-TDP-43 using established criteria for FTLD (Cairns et al., 2007; Bigio, 2008; Mackenzie et al., 2010). The most common FTLD, FTLD with TDP-43-positive inclusions, FTLD-TDP, was defined by TDP-43-positive neuronal cytoplasmic and intranuclear inclusions, dystrophic neurites and glial cytoplasmic inclusions in the superficial layers of cerebral cortex and dentate gyrus. The diagnosis of FTLD-tau, which includes progressive supranuclear palsy, corticobasal degeneration and Pick's disease, was defined by the specific patterns of p-tau glial and neuronal pathology and neuroanatomical areas of involvement according to consensus criteria (Litvan et al., 1996; Cairns et al., 2007; Dickson, 2009).

If criteria for more than one neurodegenerative disease were present, the case was considered to be mixed disease. Diagnosis of

multiple system atrophy was based on published criteria (Dickson et al., 2009).

Semi-quantitative assessment of neuropathological features

The density of neurofibrillary tangles, astrocytic tangles, diffuse and neuritic amyloid– β plaques and vascular amyloid was rated semi-quantitatively using AT8 or amyloid- β immunostained paraffinembedded 10 μ m sections according to methods previously reported (McKee *et al.*, 2006).

Apolipoprotein E genotyping

Apolipoprotein E (ApoE) genotyping was conducted using restriction isotyping for determining ApoE isoforms based on brain tissue samples.

Statistical analysis

Stage of CTE was treated as an inexact ordinal variable; Spearman's rank order correlation was used to determine the statistical dependence between CTE stage and all linear variables of interest (e.g. age, years of education, total number of reported concussions, total number of years of American football played and number of years between retirement and death). For non-linear independent variables, the Wilcoxon–Mann–Whitney two-sample rank-sum test was used for

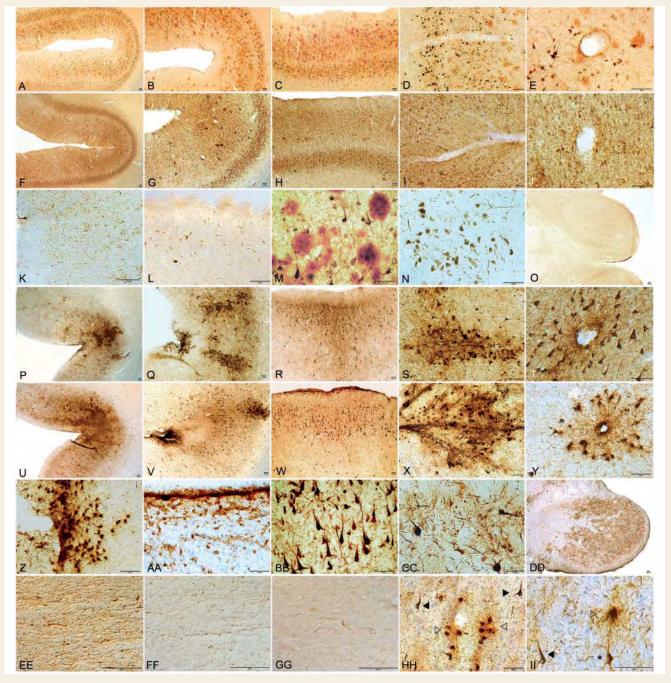


Figure 1 Distinctive p-tau pathology of CTE compared with Alzheimer's disease. (A-O) Alzheimer's disease. (A-C) Double immunostained sections for amyloid-ß (red) and PHF-1 (brown) show diffuse cortical distribution of neurofibrillary tangles preferentially involving laminae III and V and without accentuation at depths of sulci. (D and E) Small blood vessels at sulcal depths show no clustering of neurofibrillary pathology perivascularly. (F and G) Sections immunostained for AT8 demonstrate diffuse cortical distribution of p-tau pathology without accumulations at sulcal depths. (H) Neurofibrillary tangles are preferentially distributed in laminae III and V. (I and J) Small blood vessels at bottom of cortical sulcus show no clustering of neurofibrillary pathology around vasculature (AT8 immunostain). (K) Subpial region at depth of sulcus shows no p-tau positive astrocytic tangles (AT8 immunostain). (L) Periventricular region of third ventricle shows no ependymal immunostaining for p-tau and low densities of p-tau neurites (AT8 immunostain). (M) Double immunostained section showing abundant amyloid-ß plaques (red) and interspersed PHF-1 neurofibrillary tangles (brown). (N) Moderate neurofibrillary change in substantia nigra pars compacta typical of severe Alzheimer's disease (AT8 immunostain). (O) Absence of astrocytic tangles or neurofibrillary tangles in mammillary body in Alzheimer's disease (AT8 immunostain). (P-FF) CTE. (P-R and U-W) Sections immunostained for AT8 showing irregular cortical distribution of p-tau pathology with prominent subpial clusters of p-tau astrocytic tangles, focal accentuation at depths of sulci and distribution of neurofibrillary tangles in superficial cortical laminae II-III. (S, T, X and Y) Small blood vessels at bottom of cortical sulcus prominent perivascular distribution of astrocytic tangles and neurofibrillary tangles (AT8). (Z) Subpial region at depth of sulcus shows prominent cluster of AT8 positive astrocytic tangles. (AA) Periventricular region of third ventricle shows

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independent variables with only two groups (e.g. lifetime history of steroid use, presence of at least one ApoE e4 allele), whereas the Kruskall–Wallis test was used for variables with more than two groupings (e.g. position played).

Additionally, to determine whether the proportion of individuals with at least one ApoE e4 allele was higher in individuals diagnosed with CTE, a Chi-square goodness of fit test was performed comparing all CTE cases (n = 65) with the expected proportion in the US population (Corder *et al.*, 1993).

Results

The 85 brain donors with a history of mild traumatic brain injury included 80 athletes (22 of whom were also military veterans), three military veterans with no history of contact sports, one civilian who had experienced multiple falls and one individual who engaged in self-injurious repetitive head-banging behaviour (84 males, one female, age range 14–98 years, mean 54.1 ± 23.3 years) (Table 2). We also analysed the brains of 18 cognitively

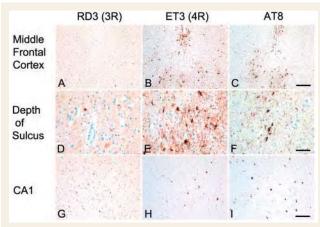


Figure 2 Patterns of 3R and 4R Tau in CTE. (**A**, **D** and **G**) 3R immunostaining shows scattered RD3 immunoreactive neurons in middle frontal cortex and CA1 hippocampus. (**B** and **E**) 4R immunostaining shows many ET3 immunoreactive neurons and astrocytic tangles in the subpial region of the middle frontal cortex and at the depth of the sulcus. (**H**) 4R immunostaining shows many ET3 immunoreactive neurons in CA1 hippocampus. (**C**, **F** and **I**) AT8 immunostaining shows 3R and 4R immunopositive neurons and astrocytic tangles in middle frontal cortex and CA1 hippocampus. All are 10 -μm paraffin-embedded sections, scale bars = $50 \, \mu m$.

intact subjects without known history of repetitive mild traumatic brain injury (17 males: one female, age range 18–88 years, mean 62.0 ± 17.4 years), seven of whom were military veterans and three of whom were athletes (skiing, sailing, golf and trap shooting) with no known history of mild traumatic brain injury.

Pathological findings

Seven of the 18 control brains were completely negative for p-tau neurofibrillary tangles (mean age 48.1 ± 19.8 years), 11 control brains showed Alzheimer's-type neurofibrillary pathology limited to the hippocampus and entorhinal cortex consistent with Braak neurofibrillary stages I and II (mean age 70.8 ± 7.8 years). Three control subjects showed small amounts of amyloid-ß deposition as diffuse, neuritic plaques or vascular amyloid (mean 69.7 ± 8.1 years). No control case showed evidence of perivascular clusters of neurofibrillary tangles or astrocytic tangles, neurofibrillary tangles localized to the depths of the cerebral sulci or neurofibrillary tangles primarily localized to the superficial cortical laminae (Table 2, Cases 1–18).

Brains from 17 of the 85 individuals with a history of repetitive mild traumatic brain injury (16 males: one female; mean age 32.6 ± 22.4 years, 20% of the mild traumatic brain injury sample) did not show any changes of CTE (Table 2, Cases 19-35). One individual who played high school football (Case 32) was diagnosed with multiple system atrophy. The brains of 68 of the 85 subjects showed p-tau immunoreactive neurofibrillary tangles and astrocytic tangles in a pattern and neuroanatomical distribution diagnostic of CTE (68 males, 0 females; mean age 59.5 ± 20.4 years, 80% of the mild traumatic brain injury sample). The 68 included 50 football players [34 of whom played professionally including 33 National Football League players (two athletes also played in the Canadian Football League and one also played in the United Football League) and one Canadian Football League player], one semi-professional football player, nine college football players, six high school football players, five hockey players (four National Hockey League players and one amateur hockey player), seven professional boxers, one amateur boxer and one professional wrestler. Four individuals without a history of contact sports also developed CTE including three veterans and one individual who displayed self-injurious head banging behaviour. CTE or CTE-MND was diagnosed in 51 cases (51 males, 0 females, mean age 55.3 \pm 21.8 years; 60% of the mild traumatic brain injury sample, 75% of all CTE cases). CTE-MND was diagnosed in eight cases (including three cases previously reported, McKee et al., 2010; 9.4% of mild traumatic

Figure 1 Continued

intense ependymal immunostaining for AT8 and abundant pericapillary neurites. (**BB**) Double immunostained section for amyloid- β (red) and PHF-1 (brown) shows dense neurofibrillary tangles without amyloid- β deposition. (**CC**) Dense AT8 immunostained astrocytic tangles and neurofibrillary tangles in substantia nigra pars compacta of severe CTE (AT8). (**DD**) Dense AT8 immunostained astrocytic tangles and neurofibrillary tangles in mammillary body typical of CTE. (**EE**) Dense CP-13 immunostained axonal varicosities and neuropil threads in the anterior commissure in CTE. (**FF**) AT8 immunostained axonal varicosities and neuropil threads in the external capsule in CTE. (**GG**) Alzheimer's disease: low densities of AT8 immunostained neuropil threads in subcortical white matter. (**HH** and **II**) CTE: AT8 immunostained astrocytic tangles (open arrowheads), neurofibrillary tangles (arrowheads) and pre-tangles (asterisk) characteristic of CTE. Some sections counter-stained with cresyl violet; all scale bars = 100 μ m.

Table 2 Demographics, pathological diagnoses and immunoreactivity of the controls and mild traumatic brain injury cohort

	- - -)	,				`				,				
Case	MTBI exposure	Age	Race	Sex	ApoE	Cause of death	CTE	Amyloid-ß			αSYN	TDP-43	Other diagnoses	
	(sport /military)	(decade)						DP	NP	CAA				
7	No athletics	10–19	I	M	n/a	Cerebral aneurysm	0							
7	No athletics	20–29	U	٤	34	Suicide	0							
n	No athletics, Vet	50–59	O	٤	n/a	Kidney failure	0							
4	No athletics, Vet	69-09	O	٤	33	Malignancy	0							
2	No athletics	20–59	U	٤	23	Malignancy	0							
9	No athletics	69-09	U	ш	n/a	Malignancy	0							
7	No athletics	69-09	U	8	33	Malignancy	0							
∞	Sailing, skiing	69-09	U	٤	23	Malignancy	0							
0	Trapshooting, Vet	69-09	U	٤	33	MVA	0							
10	Skiing, hiking, golfing, Vet	69-09	U	٤	33	Malignancy	0							
7	No athletics	69-09	U	×	24	ICH	0	++++	+	+				
12	No athletics, Vet	69-09	U	×	34	Cardiac	0	+++	+					
13	No athletics, Vet	70-79	U	×	23	Malignancy	0							
14	No athletics	70–79	U	×	23	Malignancy	0							
15	No athletics, Vet	70–79	U	×	33	ICH	0	+++	++	+				
16	No athletics, Vet	70-79	U	×	33	Cardiac	0							
17	No athletics	70–79	U	٤	33	Respiratory failure	0	+						
18	No athletics	80–89	U	×	23	Cardiac	0							
19	MS soccer	10–19	U	×	33	Cerebral oedema	0							
20	HS AFB	10-19	U	×	33	Overdose	0							
21	HS AFB	10–19	U	×	33	Overdose	0							
22	HS AFB	10-19	U	×	34	Suicide	0							
23	College hockey	10–19	U	٤	33	Overdose	0							
24	HS AFB	10–19	U	×	33	Cardiac	0							
25	Pro ice hockey	20–29	U	۶	n/a	Metabolic encephalopathy	0							
56	HS AFB	20–29	U	₹	n/a	dSW	0							
27	Pro AFB	20–29	U	×	33	dSW	0							
28	HS AFB	20–29	U	₹	33	Suicide	0							
29	MMA	20–29	U	٤	33	Suicide	0							
30	Pro wrestling	30–39	U	×	33	Suicide	0							
31	Comp skiing	30–39	U	ш	34	Suicide	0							
32	HS AFB	40-49	O	٤	n/a	Suicide	0						MSA	
33	HS baseball, hockey, Vet	69-09	U	٤	n/a	Malignancy	0							
34	Youth box	70–79	U	٤	23	Cardiac	0							
35	Firefighter	80–89	U	٤	34	Respiratory failure	0							
36	HS AFB, HS basketball	10–19	U	٤		SIS	_					+		
37	HS AFB, rugby	10–19	U	×	33	Cerebral oedema	_					+		
38	IED/explosives, HS AFB, Vet	20–29	I	×	33	ICH	_							
39	Pro AFB	20–29	ΑA	×	33	Suicide	_					+		
40	HS AFB, Vet	20–29	U	٤	34	Suicide	_							
41	Pro AFB	30–39	U	٤	33	Cardiac	_					+		
42	Pro AFB	20–29	U	٤	34	Malignancy	_							
43	College AFB	20–29	U	٤	34	Suicide	=					+		
4	Pro wrestling	20–29	U	٤	33	Overdose	=							
45	Pro ice hockey	20–29	U	8	33	Overdose	=					+		
46	College AFB,	30–39	U	٤	33	Respiratory failure	=					+ + +	CTE-MND	
	ns wiesumg													
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Case	(sport /military)	(decade)	Nace	Y D	2	Cause of death	3	DP	NP NP	CAA	2 5	f 5	Other dragnoses
į			(:	0	-	:	i		:			
47	IED, HS AFB, Prison	30–39	O	≥	33	Overdose	=					+	
48	College AFB	40-49	¥	٤	33	Respiratory failure	=					++++	CTE-MND
49	IED, MVA, Vet	40-49	U	٤	33	Cerebral aneurysm	=					0	
90	Pro ice hockey	40-49	O	٤	33	Cardiac	=					+	
51	Pro AFB	40-49	U	٤	33	Cardiac	=					0	
52	HS AFB	40-49	U	٤	33	Suicide	=					+	
53	Pro AFB	40-49	¥	٤	34	Respiratory failure	=					+++++	CTE-MND
54	College AFB	65-05	O	٤	33	Malignancy	=			++		+	
25	Pro ice hockey	65-05	U	٤	34	Cardiac	=					+	
99	Pro AFB, Vet	80-89	O	٤	33	Cardiac	=	+ + + +	+			+	
22	Pro AFB	30–39	U	٤	33	Suicide	≡					0	
28	Pro box	40-49	U	٤	33	Suicide	≡					+	
69	HS basketball, college AFB,	40-49	O	٤	33	Respiratory failure	≡					+++++	CTE-MND
(amateur box, Vet	((:	(-	:						
9 ;	College AFB	40–49	، ر	≨ :	33	Overdose	≣ :					+ (
61	Pro AFB	40-49	U	٤	4	dSW	=					0	
62	Pro AFB	40-49	U	٤	44	Overdose	=	+				0	
63	Pro AFB	69-09	¥	٤	34	Suicide	≡					+	
64	Pro AFB	50-59	U	٤	34	Cardiac	≡					+	
65	Self-injury	50-59	U	٤	n/a	Respiratory failure	≡					0	
99	Pro AFB	69-09	O	٤	23	Respiratory failure	≡					+ + + +	CTE-MND
29	Pro AFB	69-09	Ą	٤	33	Overdose	≡					+	
89	Pro AFB	69-09	O	٤	33	Cardiac	≡					+	
69	Pro AFB	69-09	U	٤	33	Respiratory failure	≡					++++	CTE-MND
70	TBI, PT epilepsy, Vet	70-79	O	٤	33	Pneumonia	=	+++	+++	+++		+	
71	MVA, altercation, Vet	80–89	U	٤	33	Pneumonia	≡	+				+	
72	Pro box	69-09	Ą	٤	33	Respiratory failure	≥					+	
73	Pro box	69-09	U	٤	34	Respiratory failure	≥	+	+			++++	CTE-MND
74	Pro box	69-09	U	٤	33	Cardiac	≥	+++	+			++++	CTE-MND
75	Pro box, Vet	70-79	U	٤	33	E	≥					+ + +	
9/	Pro AFB	70–79	¥	٤	34	Malignancy	≥					++++	
17	Pro AFB	70-79	U	٤	23	Cardiac	≥					+++	
78	Pro AFB, Vet	80-89	¥	٤	44	Respiratory failure	≥	+		+ + + +		++++	
79	Pro box, Vet	70-79	¥	٤	33	FT	≥	+	+		+	++++	
80	Pro AFB, Vet	70-79	U	٤	33	Respiratory failure	≥	++	+	+		++++	
81	Pro box	80–89	¥	٤	34	Sepsis	≥	+	++	+		++++	
82	Pro AFB	80–89	U	٤	33	FT	≥					+	
83	Pro AFB, Vet	68-08	¥	٤	33	FH	≥	+	+			+ + + +	
84	Semi Pro AFB, Vet	68-08	U	٤	33	Ħ	≥	+ + + +	+	+		++++	
85	Amateur box, Vet	66-06	U	٤	n/a	Ħ	≥	+++	+++	+++		+ + + +	
98	Pro AFB, Vet	66-06	U	٤	33	FIT	≥				+	+ + + +	
87	College AFB	69-09	U	٤	4	FIT	≥	+++++	+ + + +	++	+	+	Alzheimer's disease
88	Pro AFB, Vet	69-09	U	٤	23	FT	≥	+ + + +	++++	++		+	Alzheimer's disease
68	College AFB	69-09	U	٤	33	FT	≥	+ + + +	+ + + +	++++	+	+	Alzheimer's disease
90	Pro AFB, Vet	70-79	U	٤	34	FIT	≥	++++	++	+		++++	Alzheimer's disease
91	Pro AFB	69-09	U	٤	33	FTT	≥	+ + +	++	+++	+ + +	+	Alzheimer's disease, Parkinson's disease
													(00:10:4000)

ewy Body disease Alzheimer's disease, -ewy Body disease Parkinson's disease, Parkinson's disease, ewy Body disease ewy Body disease ewy Body disease Parkinson's disease Other diagnoses FTLD-TDP FTLD-TDP Pick's rDP-43 ×SYN CAA ٩ Amyloid-B Ы 3 \geq \equiv \equiv \equiv Respiratory failure failure of death Respiratory Malignancy Cardiac Cardiac Cardiac Cause E E E F ApoE 34 33 2 4 4 33 23 33 Sex **\$ \$ \$ \$** 70-79 70-79 70-79 70-79 70-79 70-79 Vet College AFB, college rugby, Amateur ice hockey, Vet (sport /military) MTBI exposure Pro ice hockey Canadian AFB Pro AFB, Vet Pro AFB, Vet Pro AFB Pro AFB Pro AFB Pro AFB Pro AFB Pro AFB Case 100 101 102 92 66 96 97 98

able 2 Continued

FTT = failure to thrive associated with dementia; GSW = gunshot wound; H = Hispanic; HS = high school; ICH = intracerebral haemorrhage; IED = improvised explosive device blast exposure; LBD = Lewy body disease; M = male; CAA = cerebral amyloid angiopathy; Comp = competitive; DP = diffuse amyloid ß plaques; F = female; FB = football; MS = middle school; MTBI = mild traumatic brain injury; MVA = motor vehicle accident; MSA = multiple system atrophy; n/a = not available; NP = neuritic amyloid ß plaques; Pick's = Pick's disease; PT = post-traumatic; SIS = second impact syndrome; TBI = traumatic brain injury; TDP43 = TAR DNA-binding protein; Vet = military veteran. Scoring scale: + = mild, C = Caucasian; AFB = American football; α SYN = alpha-synuclein; AA = African American; Box = Boxing; = progressive supranuclear palsy; Pro = professional; SP

brain injury sample, 11.8% of CTE cases) (Table 2). The brains of seven subjects fulfilled criteria for CTE plus Alzheimer's disease (mean age 69.9 ± 6.5 years, 8.2% of mild traumatic brain injury sample, 10.3% CTE cases); 11 were diagnosed with CTE plus Lewy body disease (mean age 73.4 ± 6.2 years; 12.9% of the mild traumatic brain injury sample, 16.2% of CTE cases), either as Parkinson's disease, transitional or diffuse Lewy body disease; and four (mean age 75.5 ± 5.0 years; 4.7% of the mild traumatic brain injury sample, 5.9% of CTE cases) were diagnosed with CTE plus FTLD [FTLD-TDP in two, FTLD-tau in two (progressive supranuclear palsy and Pick's disease in one each)] (Table 2).

Amyloid-B and Lewy bodies

Amyloid-ß deposition, either as diffuse plaques, neuritic plaques or vascular amyloid, was found in 30 brains (35.3% of the mild traumatic brain injury sample, 44.1% of CTE cases) and 14 (27.4%) pure CTE cases. Subjects with CTE and pure CTE whose brains showed amyloid-ß deposits were significantly older than those without amyloid- β (P < 0.0001; P < 0.0001). Alpha-synucleinpositive Lewy bodies were found in 15 of the CTE cases (22.0%). In two cases with CTE, Lewy bodies were restricted to the olfactory bulb and medulla, and in two cases with CTE plus Alzheimer's disease, Lewy bodies were restricted to the amygdala. Subjects with Lewy bodies were significantly older than those without (P = 0.03).

Neuropathology of chronic traumatic encephalopathy

In individuals with CTE or CTE-MND, 13 had diffuse plaques (25.5%), 10 had modest numbers of neuritic plaques (19.6%) and seven had small amounts of vascular amyloid (13.7%). These 51 brains showed a predictable range of unique p-tau pathology that could be divided into four distinct stages of disease (Figs 1-3). CTE disease severity ranged from very mild (stage I/IV, n = 7, age range 17-56 years, mean 28.3 years \pm 13.5), mild (stage II/IV, n = 14, age range 21–87 years, mean 44.3 years \pm 16.7), moderate (stage III/IV, n = 15, age range 38-82 years, mean 56.0 years \pm 14.2) to severe (stage IV/IV, n = 15, age range 51–98 years, mean 77.4 years \pm 11.7) (Table 2 and Supplementary Tables 3 and 4). The p-tau neurofibrillary tangles at all stages were immunoreactive for both 3 R and 4 R tau, and astrocytic tangles were predominantly immunoreactive for 4R tau (Fig. 2).

Stage I chronic traumatic encephalopathy

Seven brains showed stage I CTE (Table 2, Cases 36-42, Figs. 3 and 4, Supplementary Tables 2 and 3). Mild lateral ventricular enlargement was found in three of the five intact brain specimens. The gross neuropathological features and brain weights were otherwise unremarkable (mean brain weight 1463.3 \pm 179.0 g). Microscopically, stage I was characterized by focal epicentres of perivascular p-tau neurofibrillary and astrocytic tangles, most prominent in the sulcal depths and typically affecting superior and dorsolateral frontal cortices (Figs 1-3). The cortex surrounding

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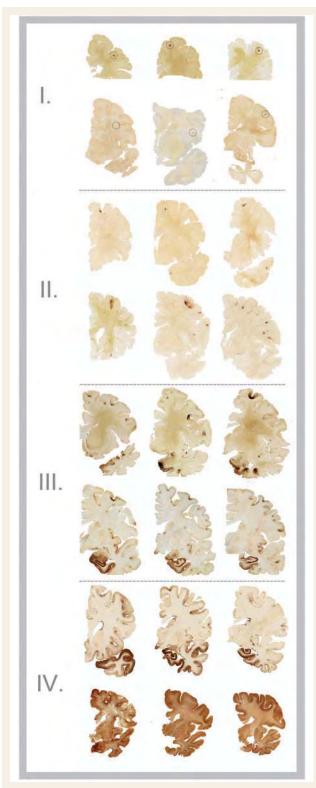


Figure 3 The four stages of CTE. In stage I CTE, p-tau pathology is restricted to discrete foci in the cerebral cortex, most commonly in the superior, dorsolateral or lateral frontal cortices, and typically around small vessels at the depths of sulci (black circles). In stage II CTE, there are multiple epicentres at the depths of the cerebral sulci and localized spread of neurofibrillary pathology from these epicentres to the superficial layers of adjacent cortex. The medial temporal lobe is

the epicentres was unremarkable except for rare isolated neurofibrillary tangles in superficial laminae. Low densities of neurofibrillary tangles were found in the locus coeruleus in two cases. One case showed sparse neurofibrillary tangles in the hippocampus, entorhinal cortex and substantia nigra; another case displayed p-tau neurofibrillary tangles and distorted axonal profiles in the medulla (Case 37). Phosphorylated neurofilament immunohistochemistry showed scattered distorted axonal varicosities in frontal cortex, subcortical white matter and deep white matter tracts of the diencephalon, which were also occasionally immunoreactive for p-tau (Fig. 4). TDP-43 immunopositive neurites were found in four of the seven cases (57%) in the frontal subcortical white matter and fornix.

Clinical symptoms

Family interview and medical record review were available in six of the seven subjects with stage I CTE. One subject was asymptomatic. Four of the six reported headache and loss of attention and concentration, three reported short-term memory difficulties, aggressive tendencies and depression and two reported executive dysfunction and explosivity. Two subjects were diagnosed with post-traumatic stress disorder (Tables 3 and 4).

Stage II chronic traumatic encephalopathy

Fourteen brains showed stage II pathology (Table 2, Cases 43-56). Grossly, there was no evidence of cerebral atrophy with a mean brain weight of 1463.3 \pm 100.1 g. There was mild enlargement of the frontal horn of the lateral ventricles or third ventricle in 6 of the 11 intact specimens, and a small cavum septum (0.2-0.7 cm) was found in four; the third ventricle was enlarged and sharply concave in three. Three cases showed pallor of the locus coeruleus and substantia nigra. There was severe gliosis and atrophy of one mammillary body in one case (Case 45). P-tau pathology was found in multiple discrete foci of the cortex, most commonly superior, dorsolateral, lateral, inferior and subcallosal frontal, anterior, inferior and lateral temporal, inferior parietal, insular and septal cortices. Neurofibrillary tangles were also found in the superficial layers of cortex (Figs. 1 and 3). Moderate densities of neurofibrillary tangles were also found in the locus coeruleus, nucleus basalis of Meynert and amygdala even in the younger individuals (Fig. 4 and Supplementary Table 3). Low densities of p-tau neurofibrillary tangles and

Figure 3 Continued

spared neurofibrillary p-tau pathology in stage II CTE. In stage III, p-tau pathology is widespread; the frontal, insular, temporal and parietal cortices show neurofibrillary degeneration with greatest severity in the frontal and temporal lobe, concentrated at the depths of the sulci. Also in stage III CTE, the amygdala, hippocampus and entorhinal cortex show neurofibrillary pathology. In stage IV CTE, there is severe p-tau pathology affecting most regions of the cerebral cortex and the medial temporal lobe, sparing calcarine cortex in all but the most severe cases. All images, CP-13 immunostained 50- μ m tissue sections.

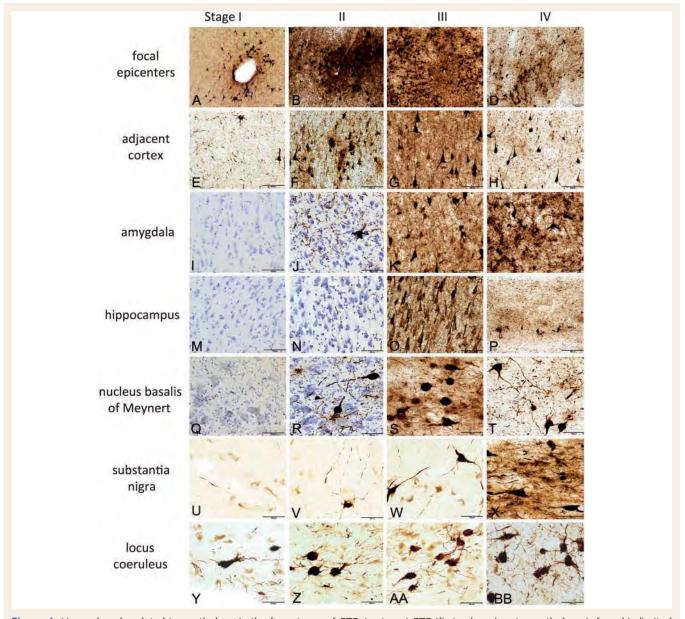


Figure 4 Hyperphosphorylated tau pathology in the four stages of CTE. In stage I CTE (first column), p-tau pathology is found in limited discrete perivascular foci (A), typically at the depths of sulci or around small vessels. There is mild p-tau pathology in cerebral cortices neighbouring the epicentres (E). There is no or minimal p-tau pathology in the amygdala (I) or CA1 of hippocampus (M). Occasional p-tau neurites are found in the nucleus basalis of Meynert (Q) and substantia nigra (U); isolated neurofibrillary tangles are present in the locus coeruleus (Y) in stage I. In stage II CTE (second column), there is spread of pathology from focal epicentres (B) to the superficial layers of adjacent cortex (F). The medial temporal lobe shows only mild neurofibrillary pathology, including amygdala (J) and CA1 hippocampus (N). Nucleus basalis of Meynert (R) and locus coeruleus (Z) demonstrate moderate p-tau pathology as neurofibrillary tangles and neurites; the substantia nigra (V) shows only modest pathology. In stage III, p-tau pathology is severe and widespread throughout the frontal, insular, temporal and parietal cortices. The cortical epicentres and depths of the sulci often consist of confluent masses of neurofibrillary tangles and astrocytic tangles (C). The intervening cortices show advanced neurofibrillary degeneration (G). The amygdala (K), hippocampus (O) and entorhinal cortex demonstrate marked neurofibrillary pathology. The nucleus basalis of Meynert shows dense neurofibrillary tangles (S); the locus coeruleus (AA) shows advanced neurofibrillary pathology, and the substantia nigra is moderately affected (W) in stage III CTE. In stage IV CTE, there is widespread p-tau pathology affecting most regions of the cerebral cortex and medial temporal lobe with relative sparing of the calcarine cortex. Astrocytic tangles are prominent, and there is marked neuronal loss in the cortex, amygdala and hippocampus. Phosphorylated-tau neurofibrillary tangles are reduced in size and density. The cortical epicentres show severe neuronal loss and prominent astrocytic tangles (D); similar changes are found throughout the frontal, temporal and parietal cortices (H). The amygdala demonstrates intense gliosis and p-tau neuronal and glial degeneration (L). The hippocampus is sclerotic with marked neuronal loss, gliosis, ghost neurofibrillary tangles and astrocytic tangles (P). The nucleus basalis of Meynert shows marked neurofibrillary pathology and gliosis (T); the substantia nigra (X) and locus coeruleus (BB) show advanced neurofibrillary pathology. All images: CP-13 immunostained 50 - µm tissue sections, some counterstained with cresyl violet, all scale bars = 100 µm.

	•								
Case	Years of education	Family history of neurological disease	Age of symptom onset	Presenting symptoms	Headache	Depression	Impulsivity	Explosivity	Aggression
Stage 1	CTE								
36	11	None	17	HA	++				
37	12	None	18	HA	++				
38	12	None	20	НА	++	++		++	++
39	14	None	26	ATT, STM, LANG		+	+		+
4	16	None	30	HA, STM	++	++		++	+
42	16	Mother: Alzheimer's disease	n/a	None					
Stage II	CTE								
43	15	None	n/a	None			+		
44	11	None	26	HA, STM	++	++		++	+++
45	11	None	26	HA, STM, MS	++	++	++	++	+++
46	16	None	30	MND		++	+	++	+++
47	13	None	31	STM, DEP, PTSD		++	+++		
48	17	None	40	MND	+	++	+	+++	
49	16	None	42	HA, DEP, ATT	++	++			
20	1	None	14	STM, ATT, EXP, EXEC	+	+		++	+++
51	20	None	46	HA	++	+			
52	16	Father: possible Alzheimer's	47	STM, ATT, EXEC, DEP		+++		+	+
53	12	usease, pipulai usease Father: possible undiagnosed	48	MND		+++		+	+
54	14	None	52	HA, STM	++	++	+	+++	+++
55	13	None	n/a	None				+	+
99	18	None	n/a	None				+	
Stage III	II CTE								
57	14.5	None	34	HA, MS, PAR	+++	+	++	+	+++
28	15	None	37	HA, psychosis, STM	+++	+++	+++	+++	+++
29	16	None	27	MND		+			
09	16	None	38	STM, DEP, EXP		++	++	++	++
61	14	None	40	STM, ATT, EXEC, EXP				++	
62	16	Father: bipolar disease	42	ATT, EXEC		+			
63	18	Father: Alzheimer's disease	45	HA, EXP	++	++	+	+++	+ +
64	16	None	53	STM, ATT, EXEC	+	+		+++	
99	16	None	99	STM, apathy				+++	+++
29	16	Brother: mental illness	63	STM, EXEC, ATT		+			
89	15	None	n/a	None		+		+	+
69	18	Father: depression	52	HA, STM, DEP, IMP	++	++	++		
Stage IV	v CTE								
72	12	None	42	AGG, DEP, PAR		+++		+	+ +
73	15	None	46	EXEC, IMP, PAR, AGG		++	+++	+++	+ +
74	12	Sibling: ALS	64	STM, EXEC, PAR			+++	+++	+ +
									(benditable)

Table 3 Continued

rears or education	T Family nistory or on neurological disease	Age or symptom onset	Presenting	неадаспе	Depression	Impulsivity	Depression Impulsivity Explosivity Aggression	Aggression
2	None	56	STM, DEP, AGG, EXP		++	+	+++	+++
2	None	35	PAR, IMP, BIZ		++	++	+++	+++
9	Mother: bipolar disease	58	DEP, AGG		++	++	+++	++
∞	None	09	STM, EXEC, BIZ					
9	None	92	STM, EXEC, LANG		++		+	+
12	Brother: Alzheimer's disease	35	STM, ATT, Falls			++	++	++
8	None	49	ATT, AGG, EXP	+++	++		++	++
10	None	92	AP, EXEC, EXP				++	++
16	None	74	PAR	++			+	+
9	None	83	STM, EXEC					

BIZ = bizarre behaviours; DEP = Depression; EXEC = executive dysfunction; EXP = explosivity; HA = headaches; IMP = impulsivity; LANG = language disturbance; MS = mood swings; n/a = not applicable; PAR = paranoia; PTSD = post-traumatic stress disorder; STM = short-term memory loss. AGG = aggression; ALS = amyotrophic lateral sclerosis; ATT = attention loss;

pretangles were present in the hypothalamus, CA1 of hippocampus, entorhinal cortex, thalamus, substantia nigra and dorsal and median raphe nuclei of the midbrain. Distorted axonal varicosities, some p-tau immunoreactive, were found in frontal and temporal cortices as well as white matter tracts (Figs. 1 and 5). Eleven of the 14 subjects with stage II CTE also showed TDP-43 immunopositivity (79%). TDP-43 immunopositivity consisted of rare neurites or inclusions in the cerebral subcortical white matter, brainstem or medial temporal lobe in eight cases, often in a subpial, periventricular or perivascular distribution (Fig. 6). Three subjects showed severe TDP-43 abnormalities as neuronal and glial inclusions and neurites in widespread regions of the CNS, including the cerebral hemispheres, basal ganglia, diencephalon, brainstem, anterior horn cells and white matter tracts of the spinal cord (Fig. 6). These cases also demonstrated degeneration of lateral and ventral corticospinal tracts of the spinal cord and marked loss of anterior horn cells from the spinal cord; features that support the diagnosis of CTE-MND.

Clinical symptoms

Eleven of the 14 individuals with stage II CTE were symptomatic; common presenting symptoms were depression or mood swings, headaches and short-term memory loss. Three subjects presented with symptoms of MND. Symptoms in stage II subjects included depression or mood lability, explosivity, loss of attention and concentration, short-term memory loss and headache. Less common symptoms included executive dysfunction, impulsivity, suicidality and language difficulties (Tables 3 and 4).

Stage III chronic traumatic encephalopathy

Fifteen brains showed stage III pathology (Table 2, Cases 57-71). Grossly, most brains showed mild cerebral atrophy with dilation of the lateral and third ventricles; mean brain weight was 1394 ± 106.7 g. Septal abnormalities were found in 5 of the 12 intact brain specimens (42%) ranging from cavum septum, septal perforations or complete absence of the septum. Seven brains showed moderate depigmentation of the locus coeruleus (58%); six showed mild depigmentation of the substantia nigra (42%). Other common gross pathological features were atrophy of the mammillary bodies and thalamus, sharply convex contour of the medial thalamus, thinning of the hypothalamic floor and thinning of the corpus callosum. Microscopically, neurofibrillary tangles were widespread throughout superior frontal, dorsolateral frontal, inferior orbital, septal, insular, temporal pole, superior middle and inferior temporal and inferior parietal cortices. There were also extensive neurofibrillary tangles in the hippocampus, entorhinal cortex, amygdala, nucleus basalis of Meynert and locus coeruleus (Supplementary Table 3). Neurofibrillary tangles were frequent in olfactory bulbs, hypothalamus, mammillary bodies, substantia nigra and dorsal and median raphe nuclei. Sparse neurofibrillary tangles were found in Rolandic, cingulate cortices, thalamus, nucleus accumbens, dorsal motor nucleus of the vagus, dentate nucleus of the cerebellum and spinal cord. Severe axonal loss and distorted axonal profiles were found in the subcortical white matter, particularly affecting the frontal and temporal cortices (Fig. 5). TDP-43 immunoreactive neurites were evident in the 56 | Brain 2013: 136; 43–64 A. C. McKee *et al.*

Table 4 Clinical symptoms associated with stages of CTE

Case	Attention	Paranoia	Executive function	Suicidal	Memory	Language	Visuospatial	Apathy	Dementia	Gait	Dysarthria	Parkinsonian	PTSD
Stage	I CTE												
36	+												
37													
38	+ +				+			+					PTSD
39	+ +		+	+ +	+ +	+							PTSD
41	+		+		+								
42													
Stage	II CTE												
43				+ +									
44	+ +				+								
45	+ +		+ +		+ +	+ +	+ +	+		_	_		
46 47	+ +		+	+ + +	+ +			+		а	a		PTSD
48	+		+	+ +	+ +	+		+		a	a		FIJU
49	++				т					а	α		
50	+ +	+ +	+ +		+ +		+ +						
51													
52	+ +		+ +	+ +	+ +	+							
53										a	a		
54	+		+ +		+	+	+	+					
55													
56													
Stage	III CTE												
57	+	+ +	+ +	+ +	+	+		+					
58	+ +	+ +	+ +	+ +	+ +	+ +	+ +		+	+	+		
59	+ +									a	a		
60	+		+		+				+				
61	+ +		+ +		+ +		+	+	+				
62	+ +		+ +		+			+	+				
63	+ +		+ +	+ +	+ +	+	+	+	+				
64	+		+		+	+	+		+				
66	+ +		+ +		+		+	+ +	+	а	a		
67	+ +		+ +		+ +		+ +		+				
68 69							+			2			
	+ IV CTE		+		+ +	+	+		+	a	a		
72	++	+ +	+ +		+ +	+	+ +	+	+ +	+	+		
73	++	++	++	+ +	++	++			++	a	a		
74	++	++	++		++	+	+ +		++	a	a	+	
75	+ +	++	++		++	+ +		+ +	++	+ +	++	+	
76	+	++	+ +		+ +				+ +				
77	+ +		++	+	++			+ + +	+ +	+			
78	+ +		+ +		+ +	+ +	+ +	+ + +	+ +	+ +	+ +	+	
80			+ +		+ +	+ +			+ +				
81	+ +	+ +		+ +	+ +	+ +	+ +		+ +	+	+	+	
82	+ +		+ +	+	+ +	+ +			+ +	+	+ +	+	
83	+ +	+ +	+ +		+ +	+ +	+ +	+ +	+ +				
84		+ +	+ +		+ +	+ +	+ +	+	+ +	+			
86	+ +		+ +		+ +	+ +	+ +		+ +				

a Gait and speech difficulties associated with MND.

cerebral cortex, medial temporal lobe or brainstem of most cases. Widespread, more severe TDP-43 neuronal and glial inclusions and neurites were found in three cases with stage III CTE diagnosed with CTE-MND.

Clinical symptoms

Family interview and medical record review were available for 12 subjects with stage III CTE; one individual was asymptomatic (Case 68). The most common presenting symptoms were memory loss,

executive dysfunction, explosivity and difficulty with attention and concentration. Other symptoms frequently found in stage III subjects were depression or mood swings, visuospatial difficulties and aggression. Less common symptoms included impulsivity, apathy, headaches and suicidality. Seventy-five per cent of subjects were considered cognitively impaired. Two subjects developed symptoms of MND after the onset of cognitive or behavioural abnormalities, another developed cognitive changes after the onset of MND (Tables 3 and 4).

PTSD = post-traumatic stress disorder.

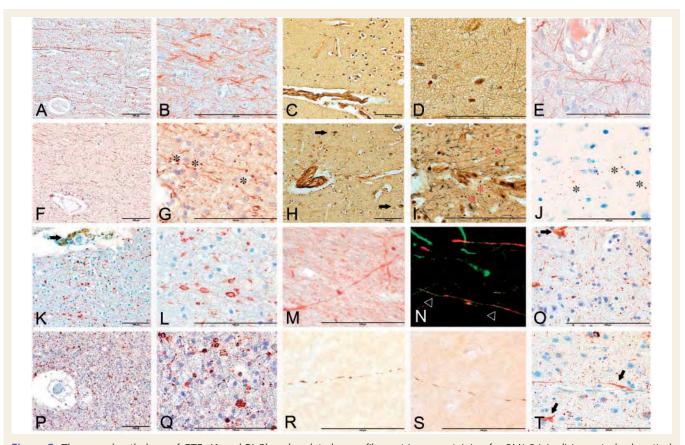


Figure 5 The axonal pathology of CTE. (A and B) Phosphorylated neurofilament immunostaining for SMI-34 (red) in control subcortical white matter shows regular alignment and linear morphology of most axonal profiles. (C and D) Axons in control cerebral cortex stained with Bielschowsky's silver method show a fine linear pattern and regularity. (E) Phosphorylated neurofilament immunostaining (SMI-34) in control cerebral cortex also shows regular alignment and linear morphology of axons even around small vessels. (F and G) Phosphorylated neurofilament immunostaining in cerebral cortex of stage II CTE demonstrates alterations in alignment and numerous rounded axonal varicosities around small vessels (asterisks). (H and I) Bielschowsky silver method in stage I CTE shows neurofibrillary tangles (arrows) and silver positive axonal varicosities (asterisks) around small arteriole. (J) SMI-34 immunostaining of same cortical focus as in H and I also shows axonal varicosities (asterisks) around cortical arteriole. (K and L) SMI-34 immunostaining in cerebral cortex of stage III CTE shows marked reduction in axonal staining and numerous large, irregular axonal varicosities. A small arteriole shows marked infiltration with haemosiderin-laden macrophages (arrow). (M) Axonal varicosities and irregularities are also found in stage I CTE. (N) CTE stage II double immunostained for phosphorylated tau (PHF-1, brown) and phosphorylated neurofilament (SMI-34, red) shows axonal swellings in continuity with phosphorylated tau neuritic abnormalities. (O) Double immunofluorescence staining for phosphorylated neurofilament, SMI-34 (red) and PHF-1 (green) in the subcortical white matter of CTE stage III demonstrates contiguous axonal varicosities (red) as well as p-tau (green) (arrowheads) in the axon. (P and Q) SMI-34 immunostaining in subcortical white matter of stage IV CTE shows severe axonal loss and multiple large, irregular axonal varicosities. (R and S) Phosphorylated tau (AT8, brown) immunoreactive irregular axonal profiles found in deep white matter tracts CTE stage I. (T) Dense axonal varicosities, distorted axonal profiles and neurofibrillary tangles (arrows) characterize the cerebral cortex of CTE stage IV immunostained with phosphorylated neurofilament (SMI-34). Images from 10 μm tissue sections, scale bars = $100 \, \mu \text{m}$, except **O** = $10 \, \mu \text{m}$.

Stage IV chronic traumatic encephalopathy

Fifteen individuals were considered to have stage IV CTE (Table 2, Cases 72-86). Macroscopic brain changes included atrophy of the cerebral cortex and white matter and marked atrophy of the medial temporal lobe, thalamus, hypothalamus and mammillary body. Mean brain weight was significantly smaller than lower stage CTE (1208 \pm 168.1 g; P < 0.001). Most brains showed ventricular enlargement, a sharply concave contour of the third ventricle, cavum septum pellucidum ranging in size from 0.5 to

1.0 cm, and septal perforations or septal absence. Pallor of the locus coeruleus and substantia nigra were found in all instances where it could be assessed. Microscopically, there was striking neuronal loss in the cortex, hippocampal sclerosis affecting CA1 and subiculum and astrocytic p-tau pathology. Severe p-tau abnormalities were found widely distributed throughout the cerebrum, diencephalon, basal ganglia, brainstem and spinal cord (Figs 1-4). Primary visual cortex was relatively spared. Subcortical white matter tracts showed marked axonal loss and distorted axonal profiles (Fig. 5). TDP-43 immunoreactivity was severe in most cases consisting of dense TDP-43 positive rounded and threadlike

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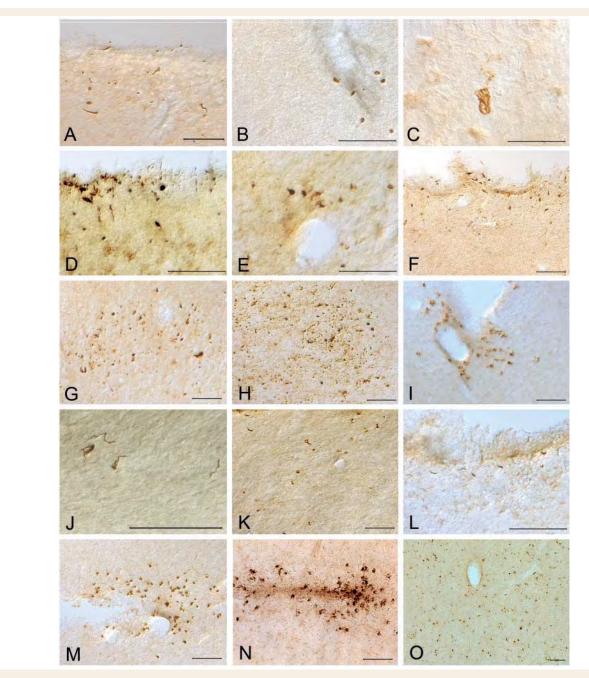


Figure 6 The phosphorylated TDP43 pathology of CTE and CTE-MND. (A) pTDP-43 immunostained neurites found in periventricular region of the third ventricle in CTE II. (B) CTE stage II demonstrating pTDP-43 immunostained neurites in a perivascular distribution. (C) pTDP-43 immunoreactive inclusion in locus coeruleus in CTE stage II. (D) Clusters of pTDP-43 immunoreactive neurites in the subpial region of the brainstem in stage III CTE. (E) Perivascular pTDP-43 neurites in stage III CTE. (F) Subpial pTDP-43 neurites in the corpus callosum of stage IV CTE. (G) Dense pTDP-43 abnormalities in the temporal cortex of stage IV CTE-MND. (H) Dense pTDP-43 pathology of CA1 hippocampus in stage IV CTE. (I–O) (I) perivascular focus at sulcal depth pTDP-43 abnormalities are widespread throughout the CNS in CTE associated with MND (CTE-MND) (J, corpus callosum; K, cerebral peduncle; L, fornix; M, subpial region of frontal cortex; N, perivascular region frontal cortex; O, Rolandic cortex). All images: 50-μm tissue sections, all scale bars = 100 μm.

neurites, intraglial and intraneuronal inclusions in cerebral cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem and, less frequently, spinal cord. Subpial, periventricular and perivascular TDP-43 immunoreactive neurites were also present (Fig. 6). In the most severely affected cases, there were dense cortical TDP-43 inclusions and neurites in all neocortical layers,

particularly layer II, as well as occasional TDP-43-positive inclusions in the dentate fascia of the hippocampus.

Clinical symptoms

Family interview and medical record review were available on 13 subjects with stage IV CTE; all were symptomatic. Executive

dysfunction and memory loss were the most common symptoms at onset, and all developed severe memory loss with dementia during their course. Most subjects also showed profound loss of attention and concentration, executive dysfunction, language difficulties, explosivity, aggressive tendencies, paranoia, depression, gait and visuospatial difficulties. Less common symptoms were impulsivity, dysarthria and parkinsonism; 31% were suicidal at some point in their course. Two of the 13 subjects developed symptoms of MND years after developing cognitive and behavioural abnormalities.

Professional American football players

Of the 35 former professional American football players (34 National Football League and one Canadian Football League), one showed no disease (Case 27, age 26 years), three had stage I/IV disease, three had stage II/IV, nine had stage III/IV disease, seven had stage IV/IV disease, two had CTE plus Alzheimer's disease, four had CTE plus Lewy body disease, two had CTE plus Alzheimer's disease and Lewy body disease, four had CTE plus FTLD and three had CTE-MND. One National Football League player had a primary diagnosis of Pick's disease with only modest evidence of CTE (Case 102), one had a primary diagnosis of Lewy body disease with stage II CTE (Case 95) and another had a primary diagnosis of progressive supranuclear palsy with stage II CTE (Case 101). Thirty-one of the 34 former professional American football players had stage III-IV CTE or CTE plus co-morbid disease (89%). Sixteen former National Football League players had pure CTE stage III-IV (47%), 94% were symptomatic; the most common presenting symptoms were short-term memory loss, executive dysfunction and attention and concentration loss. Mean age at symptom onset was 54.1 ± 14.1 years (range 34-83 years). Positions played by National Football League players positive for CTE included offensive linemen (26%), running backs (20%), defensive linemen (14%), linebackers (14%), quarterbacks (6%), defensive backs (6%), tight ends (6%) and wide receivers (6%). Mean age at death for former National Football League players diagnosed with CTE was 67.1 \pm 16.6 years (range 38–98 years).

Professional hockey players

Of the five former professional hockey players, the brain of one young player showed no signs of CTE (age 20 years). Three of the four former National Hockey League players had stage II CTE (75%), one had stage III CTE + Lewy body disease (25%) (mean age 51.3 years, range 28-73 years); only three of the four were symptomatic at the time of death.

Exposure to football, steroid use, position played and ApoE genotype

Of the 103 subjects, 58 played football as their primary sport. Of those, 42 subjects were diagnosed with CTE or CTE-MND; the families of 35 were available for structured interview regarding athletic exposure. These 35 brain donors (mean age 50.3 \pm 23.3 years, range 17-98 years) played football for a mean of 11.9 ± 6.5 years (range 2–24 years). The number of years

played (Spearman's test, $\rho = 0.805$, P < 0.0001), years since retirement (Spearman's test, $\rho = 0.753$, P < 0.0001) and age at death (Spearman's test, $\rho = 0.806$, P < 0.0001) were significantly correlated with pathological stage of CTE. Family reported number of concussions (Spearman's test, $\rho = 0.259$, P = 0.184); years of education (Spearman's test, $\rho = 0.258$, P = 0.134), lifetime steroid use (Wilcoxon-Mann-Whitney test, P = 0.731) and position played (Kruskall-Wallis test, P = 0.407) were not significantly related to CTE stage. Furthermore, of the 68 individuals diagnosed with CTE, the proportion of the sample carrying at least one ApoE e4 allele was not significantly different than that observed in the general population (Chi-square goodness of fit, P = 0.334).

Military veterans

Sixteen of the 21 military veterans with CTE were also athletes, including eight National Football League players. Nine veterans saw combat: four in the Iraq and Afghanistan conflicts, one in the Gulf War, two in Vietnam and two in World War II. Three veterans with CTE experienced a moderate-to-severe traumatic brain injury while in service (one contusion, one intraparenchymal traumatic brain injury with persistent, poorly controlled post-traumatic epilepsy, one spinal cord injury). Three were exposed to blast from improvized explosive devices and explosive munitions; one athlete was also exposed to explosive munitions in Vietnam. Three veterans of the conflicts in Iraq and Afghanistan were diagnosed with post-traumatic stress disorder, two of whom were exposed to blast from improvized explosive devices and one who experienced repetitive concussive injuries during combat and in civilian life [four veterans of the Iraq and Afghanistan conflicts were also reported in Goldstein et al. (2012)].

Cause of death and suicide

Among the 51 subjects with CTE and CTE-MND, there were seven deaths from suicide; six others clearly expressed suicidal ideations at some point during their life (26% suicidal tendencies or completed suicide, 14% completed suicide). There were six deaths from drug or alcohol overdose (12%). The most common causes of death were respiratory failure (60% associated with CTE-MND), cardiac disease, suicide, overdose, failure to thrive associated with end-stage dementia and malignancy.

Discussion

CTE is a progressive tauopathy with distinctive clinical and pathological features that occurs after repetitive mild traumatic brain injury. Although historically, CTE has been primarily associated with boxing, CTE may also occur as a consequence of American football, hockey, wrestling, rugby and exposure to blast or concussive injury associated with military service (Corsellis and Brierley, 1959; Corsellis et al., 1973; Hof et al., 1991; McKenzie et al., 1996; Geddes et al., 1999; Omalu et al., 2005, 2006, 2010; McKee et al., 2009, 2010; Gavett et al., 2010, 2011; Costanza et al., 2011; Daneshvar et al., 2011a, b; Stern et al., 2011; Baugh et al., 2012; Goldstein et al., 2012; Saing et al., 2012). We 60 | Brain 2013: 136; 43–64 A. C. McKee *et al.*

analysed the brains of 85 individuals with a history of repetitive mild traumatic brain injury and found evidence of CTE in 80%; all males, ranging in age from 17 to 98 years (mean = 59.5 years), including 64 athletes, 21 military veterans (most of whom were also athletes) and one individual who engaged in self-injurious head-banging behaviour. The development of CTE in one individual in this series and two others in the literature in whom self-injurious head banging was the sole environmental exposure suggests that repetitive mild traumatic brain injury alone is sufficient to trigger CTE in some people (Hof et al., 1991; Geddes et al., 1999). Athletes with CTE included 50 football players (33 National Football League, one Canadian Football League, one semi-professional, nine college, six high school), four National Hockey League players, one amateur hockey player, seven professional boxers, one amateur boxer and one professional wrestler. Veterans with CTE included marines, soldiers and sailors from World War II, Vietnam, Gulf War, Iraq and Afghanistan.

Neuropathological staging of chronic traumatic encephalopathy

The evidence suggests that CTE begins focally, usually perivascularly, at the depths of the sulci in the cerebral cortex and spreads slowly over decades to involve widespread regions of neocortex, medial temporal lobe, diencephalon, basal ganglia, brainstem and spinal cord. The early, focal changes of CTE demonstrated here and by others (Hof et al 1991; Geddes et al., 1999) are distinctive from p-tau pathology of the Alzheimer type reported in some cognitively normal young adults (Braak and Del Tredici, 2011) and in association with other environmental exposures (Anthony et al., 2010). The tau isoform profile and phosphorylation state in CTE is similar to Alzheimer's disease (Schmidt et al., 2001), and the neuronal tau pathology shows immunoreactivity to both 3R and 4R tau. The astrocytic p-tau pathology in CTE is predominantly 4R tau immunopositive; however, it is topographically distinct from the 4R tau immunoreactive thorn-shaped astrocytes that have been reported in the medial temporal lobe in ageing and Alzheimer's disease (Lace et al. 2012; López-González et al., 2012).

We divided the topographically predictable pattern of p-tau pathology of CTE into four stages. Stage I was characterized by perivascular p-tau neurofibrillary tangles in focal epicentres at the depths of the sulci in the superior, superior lateral or inferior frontal cortex and was clinically associated with headache and loss of attention and concentration. In stage II CTE, neurofibrillary tangles were found in superficial cortical layers adjacent to the focal epicentres and in the nucleus basalis of Meynert and locus coeruleus. Individuals with stage II CTE experienced depression and mood swings, explosivity, loss of attention and concentration, headache and short-term memory loss. Stage III CTE showed macroscopic evidence of mild cerebral atrophy, septal abnormalities, ventricular dilation, a sharply concave contour of the third ventricle and depigmentation of the locus coeruleus and substantia nigra. There was dense p-tau pathology in medial temporal lobe structures (hippocampus, entorhinal cortex and amygdala) and widespread regions of the frontal, septal, temporal, parietal and insular

cortices, diencephalon, brainstem and spinal cord. Most individuals with stage III CTE demonstrated cognitive impairment with memory loss, executive dysfunction, loss of attention and concentration, depression, explosivity and visuospatial abnormalities. Stage IV CTE was associated with further cerebral, medial temporal lobe, hypothalamic, thalamic and mammillary body atrophy, septal abnormalities, ventricular dilation and pallor of the substantia nigra and locus coeruleus. Microscopically, p-tau pathology involved widespread regions of the neuraxis including white matter, with prominent neuronal loss and gliosis of the cerebral cortex and hippocampal sclerosis. Subjects with stage IV CTE were uniformly demented with profound short-term memory loss, executive dysfunction, attention and concentration loss, explosivity and aggression. Most also showed paranoia, depression, impulsivity and visuospatial abnormalities. Advancing pathological stage was associated with a significant decrease in brain weight and increased severity of cognitive abnormalities supporting the validity of the pathological staging scheme. In addition, pathological stage correlated with duration of exposure to American football, survival after football and age at death in those who played football.

Spread of tau pathology

Under normal conditions in the mature human CNS, tau is primarily associated with microtubules in axons, where it is neither toxic nor associated with neurofibrillary pathology. Brain trauma causes some tau to become dissociated from microtubules in axons via mechanisms that most likely include intracellular calcium influx, glutamate receptor-mediated excitotoxicity and kinase activation mediating hyperphosphorylation of intracellular tau (Genis et al., 2000; Liang et al., 2009; Chen et al., 2010; Tran et al., 2011a, b; Schoch et al., 2012). Tau dissociated from microtubules may become abnormally phosphorylated, misfolded, aggregated and proteolytically cleaved by calpains and caspases, all of which are associated with neurotoxicity (Amadoro et al., 2006; Khlistunova et al., 2006; Zilka et al., 2006). Direct and indirect evidence for interneuronal tau transfer in animal models has recently suggested that interneuronal spreading of tau pathology may be due to transfer of toxic tau species between neurons (Clavaguera et al., 2009; Kim et al., 2010; DeCalignon et al., 2012; Liu et al., 2012). This might be mediated by either a prion-like templated misfolding of tau (Guo et al., 2011; DeCalignon et al., 2012; Liu et al., 2012; reviewed by Hall and Patuto, 2012) or by calcium dysregulatory effects of oligomeric or toxic N-terminal tau in the receiving neuron (Park and Ferreira, 2005; Frost et al., 2009). Although spreading of tau pathology is generally thought to occur in association with neuronal synapses, glial to glial spread, periventricular and diffuse extracellular tau migration patterns. CSF fluid enters the brain parenchyma along the Virchow-Robin spaces surrounding penetrating arteries, and brain interstitial fluid is cleared along paravenous drainage pathways suggesting a possible spread of tau pathology through this route, similar to the clearance of amyloid-ß peptide. Recent studies have demonstrated that amyloid-ß peptide (Iliff et al., 2012). Clearance through paravenous flow and the CSF might also regulate extracellular levels of p-tau and TDP-43

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and explain the frequent perivascular, subpial and periventricular localization of these proteins.

Axonal injury and TDP-43

In addition to p-tau pathology, axonal injury was apparent in all stages of CTE, ranging from multifocal, often perivascular, axonal varicosities in the cortex and subcortical white matter in stages I-II to severe, diffuse axonal loss in the cortex and white matter in CTE stages III-IV. TDP-43 abnormalities were also found in the majority of CTE cases. In CTE stages I-III, sparse TDP-43 neurites were found in various regions of the cortex, medial temporal lobe and brainstem. In stage IV CTE, TDP-43 immunoreactivity was severe, with intraneuronal and intraglial inclusions, rounded and threadlike neurites in the cortex, white matter, diencephalon, basal ganglia and brainstem. Although it is well-established that p-tau pathology correlates with the severity of cognitive impairment in other tauopathies, such as Alzheimer's disease (Wilcock and Esiri, 1982; McKee et al., 1991; Arriagada et al., 1992), the contribution of TDP-43 proteinopathy to symptoms of CTE cannot be overlooked, especially in late stage disease. As with frontotemporal dementia, CTE usually begins with behaviour and personality changes at mid-life (mean age of onset 44.3 years, range 17- 83 ± 12.1 years). But, unlike Alzheimer's disease or frontotemporal dementia, the clinical course of CTE is slow, progressing at a rate of 11-14 years between pathological stages. In addition, it is likely that axonal dysfunction and loss contribute to the production of clinical symptoms, especially in the early stages of CTE when tau pathology is focal and unlikely to account for the headache, attention and concentration loss, and memory difficulties experienced by subjects with stage I or II disease. Although the data suggest that CTE pathology is progressive, it remains to be determined whether some individuals are relatively resilient with static or even reversible pathology. Eleven per cent of individuals with CTE were asymptomatic, with a mean age at death of 59 years (range 26-87 years) and most with stage II disease, suggesting that CTE may not progress or may not progress at the same rate in all patients.

Chronic traumatic encephalopathy plus comorbid neurodegenerative disease

Of the 68 cases with CTE, 37% had co-morbid neurodegenerative disease, including MND, Parkinson's disease or Lewy body disease, Alzheimer's disease and FTLD. Repetitive traumatic brain injury and axonal injury might trigger molecular pathways that result in the overproduction and aggregation of other proteins prone to pathological accumulation in neurodegenerative disease including TDP-43, α-synuclein and amyloid-β, thereby increasing the likelihood of MND, FTLD Lewy body disease or Alzheimer's disease. Multiple epidemiological studies have shown that trauma is a risk factor for dementia, especially Alzheimer's disease, as well as for amyotrophic lateral sclerosis and Parkinson's disease (Plassman et al., 2000; Goldman et al., 2006; Schmidt et al., 2010; Pupillo et al., 2012). In addition, CTE and the accumulation of misfolded tau aggregates may promote the aggregation of pathological proteins through cross-seeding (Johan et al., 1998; Morales et al., 2009). Cross-seeding might explain the accumulation of TDP-43

in the large majority of CTE cases, its partial immunohistochemical co-location with tau and the particularly severe deposition of TDP-43 found in advanced CTE.

Chronic traumatic encephalopathy with motor neuron disease

Most subjects with CTE-MND (63%) presented with symptoms of MND, developing cognitive and behavioural symptoms several years after the onset of motor weakness, atrophy and fasciculations. The minority presented with apathy, depression, memory loss, cognitive decline, paranoia, impulsivity or executive dysfunction 1–8 years before the development of motor neuron symptoms. There was a tendency for subjects with CTE-MND to die from respiratory insufficiency at an earlier age (53.0 \pm 14.3 years) than those without MND (55.8 \pm 23.0 years), although the difference was not significant. Individuals with MND and CTE, independent of the stage of p-tau pathology, demonstrated severe TDP-43 pathology as neuronal, glial and neuritic inclusions involving widespread regions of the CNS including motor cortex and spinal cord.

Clinicopathological correlation

Neuroanatomical areas that are preferentially affected in CTE include superior, dorsolateral and lateral frontal cortices. Pathology in these regions may underlie the clinical features of disinhibition, lack of insight and poor executive function found in subjects even at early stages of CTE. Pathological involvement of the inferior temporal lobe and amygdala might contribute to the frontal symptoms and to the irritability, impulsivity, explosivity and outbursts of aggression so commonly experienced as early manifestations of CTE. Pathology of the nucleus basalis of Meynert and septal nuclei might contribute to the cognitive symptoms. Moreover, pathology in the subcallosal and inferior orbital frontal cortex and brainstem, especially the locus coeruleus and median raphe, might be related to the common symptoms of depression and mood lability. Mammillary body, anterior thalamic and hippocampal pathology most likely play a major role in producing memory loss, cognitive impairment and eventual dementia.

Even though the brain donors were not screened for cognitive impairments, an autopsy-based case series is limited by significant ascertainment bias, as families of individuals showing behavioural or cognitive symptoms are much more likely to initiate and participate in a brain donation programme than families of normally functioning individuals. Consequently, no generalizations regarding the incidence and prevalence of CTE in living athletes and veterans can be made. Furthermore, in several of the cases, the clinical symptoms were confounded by drug and alcohol abuse; therefore, the degree to which the extensive p-tau, TDP-43 and axonal pathology and neurodegeneration is responsible for the subject's clinical presentation is unclear.

Inclusion of more rigorous control subjects, such as individuals who experienced repetitive mild traumatic brain injury and did not develop behavioural or cognitive abnormalities, will be extremely useful in future studies designed to delineate critical aspects of the traumatic exposure and susceptibility to trauma-induced neurodegeneration.

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Future prospective longitudinal studies are planned to address these limitations. For instance, by studying a large number of retired National Football League athletes prospectively and conducting neuropathological analyses at death, a control group matched on age, education, athletic history, medical comorbidities and cause of death can be used to examine differences between individuals with and without clinical and neuropathological evidence of Similarly, current studies focused on a large cohort of Iraq and Afghanistan veterans with histories of blast and concussive traumatic brain injuries and post-traumatic stress disorder will shed light on the overlap between traumatic brain injury, CTE and post-traumatic stress disorder, as well as the role of combat-associated injury in producing CTE (Goldstein et al, 2012). Clinical criteria for the diagnosis of CTE need to be established and tested. Although ApoE does not appear to be a risk factor for the development of CTE or the severity of CTE pathology in this autopsy series, large prospective population-based studies need to be implemented to address this definitively (Gandy and DeKosky, 2012). The current results establish that a distinctive pattern of neuropathological changes, previously reported primarily in boxers, can also be found in other athletes and military veterans and provide a clear impetus for future studies.

CTE is a unique neurodegenerative condition that is associated with repetitive mild traumatic brain injury. Although there are many issues that require more thorough investigation, such as how much head trauma is causative, what type, and how frequent, the age when players are most susceptible and whether some individuals are genetically more prone than others, this study clearly shows that for some athletes and war fighters, there may be severe and devastating long-term consequences of repetitive brain trauma that has traditionally been considered only mild.

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Supplementary material

Supplementary material is available at Brain online.

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EXHIBIT 6

The clinical spectrum of sport-related traumatic brain injury

Barry D. Jordan

Abstract | Acute and chronic sports-related traumatic brain injuries (TBIs) are a substantial public health concern. Various types of acute TBI can occur in sport, but detection and management of cerebral concussion is of greatest importance as mismanagement of this syndrome can lead to persistent or chronic postconcussion syndrome (CPCS) or diffuse cerebral swelling. Chronic TBI encompasses a spectrum of disorders that are associated with long-term consequences of brain injury, including chronic traumatic encephalopathy (CTE), dementia pugilistica, post-traumatic parkinsonism, post-traumatic dementia and CPCS. CTE is the prototype of chronic TBI, but can only be definitively diagnosed at autopsy as no reliable biomarkers of this disorder are available. Whether CTE shares neuropathological features with CPCS is unknown. Evidence suggests that participation in contact—collision sports may increase the risk of neurodegenerative disorders such as Alzheimer disease, but the data are conflicting. In this Review, the spectrum of acute and chronic sport-related TBI is discussed, highlighting how examination of athletes involved in high-impact sports has advanced our understanding of pathology of brain injury and enabled improvements in detection and diagnosis of sport-related TBI.

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Introduction

Sport-related traumatic brain injury (TBI) is an important public health concern and is often labelled as a 'silent epidemic'. Estimates suggest that 1.6-3.8 million sport-related TBIs occur annually in the USA alone, and this number includes injuries for which no medical care is sought.1 This estimate is likely to be conservative, however, given that many sport-related TBIs are unrecognized and unreported. Sports that are associated with an increased risk of TBI include those involving contact and/or collisions, such as boxing, American football, ice hockey, soccer, rugby and the martial arts, as well as high-velocity sports such as cycling, motor racing, equestrian sports, rodeo, skiing and roller skating. Although most sport-related TBIs occur during participation in contact-collision sports and highvelocity sports, participation in any sport carries a risk of experiencing a brain injury.

TBI can generally be classified as acute or chronic. Acute TBI is used to describe injuries that occur immediately at the time of impact, with subsequent signs and symptoms of TBI, whereas chronic TBI refers to the long-term consequences of single or multiple brain traumas. In this Review, the spectrum of acute and chronic sport-related TBI is highlighted, with particular focus on cerebral concussion, diffuse cerebral swelling (DCS, also known as second-impact syndrome), chronic traumatic encephalopathy (CTE) and chronic post-concussion syndrome (CPCS). Improved recognition

Y, USA. Competing interests

The author declares no competing interests.

of concussion through education and proper medical surveillance is of paramount importance for prevention of long-term neurodegenerative disorders in athletes who experience TBI.

Acute traumatic brain injury

For athletes involved in high-risk sports, there exists a spectrum of acute TBI pathologies that can occur (Box 1). Moderate and severe injuries such as focal brain injuries, diffuse axonal injury, skull fractures and penetrating brain injury are extremely rare in sports, but can, nonetheless, be encountered. A detailed discussion of these severe TBIs is beyond the scope of this Review, but such injuries must always be considered when managing an athlete with acute brain trauma. The most common and challenging acute brain injuries in athletes—namely, cerebral concussion and DCS—are described below.

Concussion

Concussion is defined as a complex pathophysiological process that affects the brain and is induced by traumatic biomechanical forces.²⁻⁴ A concussion typically occurs following transmission of direct or indirect impulsive forces to the head, which results in rapid onset of short-lived neurological impairments,²⁻⁴ and presents clinically with cognitive, physical and behavioural signs and symptoms (Box 2). The most frequent clinical symptoms include headache, dizziness and memory impairment. Notably, loss of consciousness is not a requirement for diagnosis of concussion. In adults, most concussions

Burke Rehabilitation Hospital, 785 Mamaroneck Avenue, White Plains, New York, 10605 NY, USA. bjordan@burke.org tend to resolve spontaneously within 7–10 days;^{5–9} in children and young adolescents, however, the recovery period can be longer.³ Rather than presenting with structural injury that can be detected using conventional structural neuroimaging, the clinical symptomatology of concussion largely reflects a functional disturbance.^{2–4}

Mechanisms of injury

Rapid acceleration and deceleration of the brain, including rotational (angular) acceleration, linear (translational) acceleration and impact deceleration, are the primary mechanism by which concussion occurs (Figure 1). Rotational acceleration occurs when biomechanical forces cause the head to rotate, potentially causing axons to stretch and tear, inducing concussion and traumatic axonal injury. Linear acceleration results from biomechanical forces that cause the head to move in the anterior-posterior direction, and is capable of producing gliding contusions in the parasagittal regions of the cerebral cortex and axonal injury in the brainstem.¹⁰ Impact deceleration occurs when the head rapidly decelerates, typically when the head strikes a playing mat or field, or an arena floor (Figure 1c). The impact can lead to coup injury (an injury on the side of the head where the impact was made) and contrecoup injury of the cerebral cortex.¹⁰ Theoretically, impact deceleration can also occur when an athlete's head rapidly decelerates when striking the body of an opposing player (Figure 1d) or fixed structures such as a goalpost, railing, tree or hockey board.

Head impact telemetry (HIT) systems, which are used to measure biomechanical forces transmitted to the brain, ¹¹ have failed to identify an 'impact threshold' for induction of concussion. Video analysis of concussions sustained by professional National Football League players indicates that the majority of blows occur to the side of the helmet and/or facemask. ¹² In nonprofessional football players, however, HIT technology reveals that most concussions result from blows to the top of the helmet. ¹¹ Biomechanical forces that are capable of causing brain injury are probably a combination of rotational, linear and/or impact decelerations.

From the point at which biomechanical forces are transmitted to the brain, multiple neuropathophysiological cascades are triggered. The initial neurometabolic cascade involves neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, changes in glucose metabolism and cerebral blood flow, and impaired axonal function.¹³ Additional cascades or processes may then initiate or result, including apoptosis, calpain–caspase activation, mitochondrial dysfunction, free radical formation, neuroinflammation, growth factor alterations, and inflammatory processes.¹⁴ Furthermore, an amyloid cascade, either with or without proper clearance of amyloid components, may be initiated.¹⁵

Detection and diagnosis

No devices that enable clinical diagnosis of concussion currently exist. Several neurodiagnostic investigations

Key points

- In high-impact sports, cerebral concussion is the most common form of acute traumatic brain injury (TBI), but other moderate and severe TBIs can occur
- Cerebral concussion is a clinical diagnosis that can present with cognitive, physical and/or behavioural signs and symptoms, and does not require loss of consciousness
- Second-impact syndrome is a rare and controversial syndrome that must be considered in the management of a young athlete with concussion
- Increased exposure to sport and advancing age are putative risk factors for the development of chronic traumatic encephalopathy (CTE)
- Antemortem diagnosis of CTE is difficult, and further research is needed to establish effective biomarkers that reflect disease activity
- Chronic postconcussion syndrome is a form of chronic TBI that is clinically distinct from CTE; neuropathological overlap between these two conditions is unknown

Box 1 | Classification of acute TBI

Diffuse brain injury

- Cerebral concussion
- Diffuse axonal injury
- Diffuse cerebral swelling

Focal brain injury

- Epidural haematoma
- Subdural haematoma
- Cerebral contusion
- Intracerebral haemorrhage
- Subarachnoid haemorrhage
- Intraventricular haemorrhage
- Subdural hygroma

Skull fracture

Penetrating brain injury

Abbreviation: TBI, traumatic brain injury.

that may assist in the physician in these cases are, however, available. Neuropsychological testing can aid in determination of the occurrence and resolution of cognitive impairment, but results of these tests should not be used as the sole basis for the decision to allow an athlete to return to play.³ Standard structural neuroimaging outcomes are typically normal in patients who are evaluated for a sport-related concussion,²⁻⁴ but new structural, functional and/or metabolic imaging technologies may be useful for detection of subtle structural or functional brain injury. For example, gradient-echo MRI sequences in one athlete with a head injury revealed evidence of microhaemorrhages—a finding that is consistent with a shear injury.¹⁶

Whether diffusion tensor imaging (DTI) is beneficial in evaluation of acute concussion remains to be determined, as studies using this methodology report variable outcomes and findings. In one study published in 2012, 17 researchers observed decreased fractional anisotropy—which is suggestive of decreased fibre-tract integrity—in one of 11 tracts in professional American football players with concussion, but found no abnormalities on susceptibility-weighted imaging (SWI), which would be indicative of prior microhaemorrhages. A 2011 study 18 found increased mean diffusivity (suggestive of axonal injury) in several white matter tracts in the left hemisphere of concussed athletes, but no differences in fractional anisotropy between concussed athletes

Box 2 | Symptoms of acute concussion

Cognitive features

- Decreased speed of information processing
- Disorientation
- Lack of awareness
- Confusion
- Amnesia or other memory impairments
- Impaired concentration
- Loss of consciousness
- · Feeling in a 'fog'

Behavioural features

- Sleep disturbance
- Irritability
- Emotional lability
- Nervousness and/or anxiety
- Psychomotor retardation
- Apathy
- Fatigue
- Easily distracted

Physical features

- Headache
- Dizziness and/or vertigo
- Nausea
- Vacant stare
- Impaired playing ability
- Gait unsteadiness and/or loss of balance
- Impaired coordination
- Diplopia and/or blurred vision
- Photophobia
- Hyperacusis
- Concussive convulsion and/or impact seizure

and controls. Similarly, no differences were observed in fractional anisotropy in children with concussion compared with controls. ¹⁹ By contrast, a case study of a concussed athlete ²⁰ reported significant and colocalized changes in fractional anisotropy and mean diffusivity voxels in the right corona radiata and right inferior longitudinal fasciculus.

Functional MRI (fMRI) has revealed altered activation patterns in athletes with concussion compared with controls. During a finger-sequencing task, concussed players exhibited marked within-subject increases in the amplitude and extent of blood oxygen level-dependent activity (indicative of high levels of brain activity) that localized primarily to the parietal, lateral frontal and cerebellar regions. Concussed athletes also showed altered activation patterns on fMRI compared with controls, even when the athletes performed as well as the controls on the given task. Furthermore, athletes who exhibited hyperactivation on fMRI demonstrated a prolonged clinical recovery.

Magnetic resonance spectroscopy is a noninvasive technique that can be used to identify neurometabolic changes in the acute postconcussion phase. 24-27 Concussed athletes had decreased levels of glutamate (a principle excitatory neurotransmitter) in the primary motor cortex (M1) and decreased levels of *N*-acetylaspartate (NAA)—a marker of neuronal integrity—in the prefrontal and M1 cortices. 24 Such metabolic changes in M1 correlated directly with severity of self-reported symptoms.

In a follow-up study, the investigators confirmed their previous findings and also noted that glutamate levels recovered in the chronic postconcussion phase.²⁵ Other researchers also observed a decrease in NAA levels relative to creatine levels in concussed athletes, but noted that the deficit completely recovered by day 30 postinjury.^{26,27} Of interest, athletes who experienced a second concussion during the recovery period were found to exhibit a further decrease in the NAA:creatine ratio and, therefore, the existence of a temporal window of metabolic brain vulnerability to further injury was postulated.²⁶

Management

Appropriate management of concussion requires the immediate removal of a player from competition and their evaluation by a health-care professional.²⁻⁴ A subsequent period of cognitive and physical rest, until the athlete becomes asymptomatic, is recommended. Once an athlete is asymptomatic and no longer receiving medications to treat or modify the symptoms of concussion, a gradual stepwise return to competition should be implemented.³ Medications used in the treatment of concussive symptoms include: analgesics, nonsteriodal anti-inflammatories, antidepressants, anticonvulsants, beta-blockers and triptans for headache; vestibular suppressants and benzodiazepines for dizziness; neurostimulants for fatigue; antiemtics for nausea; and/or medications for depression and anxiety.²⁸ Neurostimulants, selective serotonin reuptake inhibitors, and anticholinesterase inhibitors have also been used in an attempt to improve neurocognitive performance following TBI.²⁸⁻³⁰

When the athlete is asymptomatic at rest and on exertion, he or she can return to full activity. ²⁻⁴ For athletes who do not show improvement after cognitive and physical rest for a period of time (for example, 1 month), a low-level, subsymptom threshold rehabilitation and/or exercise programme may be of benefit in improving post-concussion syndrome (PCS). ^{31,32} The mismanagement of a concussion can potentially result in a persistent PCS and/or second-impact syndrome. ³³

Diffuse cerebral swelling

DCS is the pathological substrate of second-impact syndrome, and represents a rare but potentially fatal injury that can occur in athletes who sustain a second brain trauma while still symptomatic from a previous concussion. This second-hit trauma leads to a catastrophic neurophysiological response of diffuse brain swelling, cerebral oedema and brain herniation.³⁴ Second-impact syndrome is thought to arise following loss of autoregulation of cerebral blood flow, which results in vascular engorgement and subsequent increased intracranial pressure and eventual herniation.³⁴

Although considered to be a rare phenomenon, the exact frequency of second-impact syndrome is unknown. One study in the USA, however, reported 17 cases among young adults aged 21 years or younger over a 30-year period.³⁵ Second-impact syndrome has been reported

in the context of American football, boxing and ice hockey, 34,36 but its existence has been questioned. One hypothesis is that second-impact syndrome is primary DCS in response to trauma without a pre-existing injury. 36,37 Although rare, DCS remains a major concern in the management of acute concussion in young athletes, owing to the high mortality rate associated with this syndrome.

According to McCrory and Berkovic,³⁸ the following clinical criteria must be fulfilled for a definitive diagnosis of second-impact syndrome: medical review after a witnessed first impact; documentation of ongoing symptoms following the first impact up to the time of second impact; witnessed second head impact with subsequent rapid cerebral deterioration; and neuropathological or neuroimaging evidence of cerebral swelling without marked intracranial haematoma or other cause of oedema.

Chronic traumatic brain injury

Chronic TBI encompasses a spectrum of disorders that are associated with long-term consequences of brain injury. The prototype of chronic TBI is CTE—a syndrome that results from long-term neurological damage following repetitive mild TBIs. Dementia pugilistica is the boxing manifestation of CTE, but this diagnosis is typically reserved for cases in which severe dementia develops following a long boxing career. Post-traumatic parkinsonism describes a parkinsonian syndrome that occurs secondary to TBI. This form of chronic TBI includes puglistic parkinsonism—a subtype of dementia pugulistica in which rigidity and tremor predominate, and which can be identified pathologically by the abundance of neurofibrillary tangles in the absence of Lewy bodies.39 Whereas CPCS is the diagnosis given to athletes in whom postconcussive symptoms do not seem to resolve, a diagnosis of post-traumatic dementia is applied to cases that meet the clinical criteria for dementia after a single moderate or severe TBI. Posttraumatic dementia differs from CTE in that the brain injury is not repetitive but results from a single trauma that is more severe than a concussion.

Evidence suggests that participation in contact sports can increase an individual's risk of neurodegenerative disorders such as mild cognitive impairment, Alzheimer disease (AD), motor neuron disease (MND) or Parkinson disease. This association represents an additional public health concern to the issue of sport-related CTE. A survey of retired professional American football players showed an association between recurrent concussion, clinically diagnosed mild cognitive impairment and self-reported memory problems. 40 Another survey in a similar population of retired athletes revealed a significant, direct association between rate of self-reported concussion and complaints of memory changes, confusion, speech difficulties, problems remembering short lists, and difficulty recalling recent events. 41 In addition, those with a history of self-reported concussion exhibited a high frequency of headache, paraesthesias and vestibular problems that were reminiscent of a CPCS.

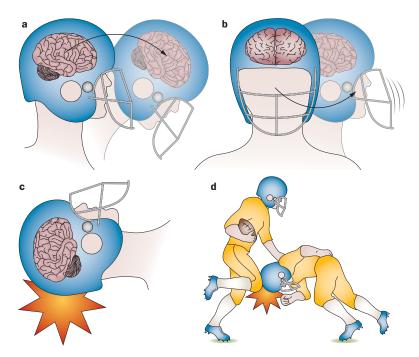


Figure 1 | Mechanisms of brain acceleration–deceleration secondary to biomechanical forces transmitted to the brain. a | Linear (translational) acceleration. b | Rotational (angular) acceleration. c | Impact deceleration. d | Impact deceleration secondary to the head striking an opposing player's body. Permission obtained from Innovative CEUs, LLC ©.

Higher AD-associated and MND-associated mortality rates were reported in retired professional American football players than in the general US population.

In contrast to the above results, however, two studies failed to identify an increased risk of neurodegeneration among participants of contact—collision sports. Comparison of a cohort of low-exposure (that is, high-school level) American football players to nonplaying individuals found no difference in the risk of dementia, Parkinson disease or MND. ⁴² In a case—control study of individuals with AD, no association was found between risk of disease and participation in contact sports, ⁴³ although this study was limited by a small sample size. Further investigation is warranted to understand the pathophysiology of chronic TBI and risk of neurodegeneration secondary to repetitive brain trauma.

Chronic traumatic encephalopathy

CTE is the long-term neurological consequence of repetitive mild TBI. The exact frequency of CTE in modern day sports is unknown but, in 1969, a landmark study of retired boxers from the UK reported a CTE prevalence of 17%. ⁴⁴ In boxing, longer duration of exposure to sport (measured as the number of bouts), older age at retirement from boxing, and longer length of boxing career, are important variables that can increase an individual's risk of developing CTE. ⁴⁴

In a subset of American football players with autopsyconfirmed CTE, a positive correlation was noted between the severity of CTE, exposure to sport, years since retirement, and age at death. ⁴⁵ Family-reported number of concussions, years of education, lifetime steroid use

Box 3 | Clinical presentations of CTE

Behavioural and psychiatric features

- Aggression and/or agitation
- Apathy
- Impulsivity
- Depression
- Delusions (such as paranoia)
- Suicidality

Cognitive features

- Impaired attention and concentration
- Memory problems
- Executive dysfunction
- Dementia
- Visuospatial difficulties
- Language impairment

Motor features

- Dysarthria, including scanning speech
- Spasticity
- Ataxia, including incoordination
- Parkinsonism, including tremors
- Gait disturbance
- Motor neuron disease (possibly)

Abbreviation: CTE, chronic traumatic encephalopathy.

Box 4 | Omalu neuropathological classification of CTE⁵¹

Phenotype

Sparse to frequent NFTs and neuritic threads in the cerebral cortex and brainstem but without involvement of the subcortical nuclei (basal ganglia) and cerebellum. No diffuse amyloid plaques in the cerebral cortex.

Phenotype II

Sparse to frequent NFTs and neuritic threads in the cerebral cortex and brainstem with or without such pathology in the subcortical nuclei (basal ganglia) and cerebellum. Diffuse amyloid plaques in the cerebral cortex.

Phenotype II

Brainstem predominant: moderate to frequent NFTs and neuritic threads in the brainstem nuclei, absent or sparse NFTs and neuritic threads in the cerebral cortex, subcortical nuclei (basal ganglia) and cerebellum. No diffuse amyloid plaques in the cerebral cortex.

Phenotype IV

Incipient: absent or sparse NFTs and neuritic threads in the cerebral cortex, brainstem and subcortical nuclei (basal ganglia). No cerebellar involvement. No diffuse amyloid plaques in the cerebral cortex.

Abbreviations: CTE, chronic traumatic encephalopathy; NFT, neurofibrillary tangle.

and position played, however, were not significantly correlated with the stage of CTE. Repetitive concussion and subconcussion has been linked to the development of CTE, 46 but a threshold of injury (that is, the number of injuries required to cause CTE) has not been established. Interestingly, the proportion of football players with CTE who were carriers of at least one apolipoprotein E (*APOE*) ϵ 4 allele—an allele associated with increased risk of AD—was not significantly different from the proportion of *APOE* ϵ 4 carriers in the general population. Other studies, however, suggest an association between the *APOE* ϵ 4 allele and chronic TBI. 47,48

Clinical presentation

Clinically, CTE can present with behavioural, cognitive and/or motor-related symptoms (Box 3). 44,45,49-54 Behavioural disturbances are often the earliest findings in CTE and can include depression, mood swings, apathy, impulsivity, aggression and suicidality. With regard to cognitive impairments, athletes can exhibit impaired attention and/or concentration, memory problems, executive dysfunction and, as the disease progresses, the individual may develop dementia. The motor manifestations of CTE—such as spasticity, tremor (parkinsonian type), ataxia, dysarthria and problems with coordination—reflect injury to the pyramidal tracts, the extrapyramidal system and the cerebellum.

MND has been noted in a subset of athletes with CTE, ^{45,50} but whether this phenotype represents a unique subtype of CTE or an overlap of two distinct disease processes, which may or may not be associated with repetitive brain injury and/or a common genetic predisposition, remains unclear. In a subset of CTE cases, headache also seems to be a prominent feature. ⁴⁵ Again, whether these cases represent comorbid CPCS (discussed below) or a distinct clinical phenotype of CTE has yet to be determined.

Pathological classification

The pathological features of CTE have been well-described and include diffuse brain atrophy, ventricular dilatation, cavum septum pellucidum with or without fenestrations, cerebellar scarring, and depigmentation and degeneration of the substantia nigra. ^{45,49–51,54,55} As the disease progresses, marked atrophy of the medial temporal lobe, thalamus, hypothalamus and mammillary bodies becomes evident.

Currently, two histopathological classifications of CTE exist. 45,51 Omalu and colleagues have identified four phenotypes of CTE (Box 4),51 whereas McKee and colleagues have classified CTE into four stages (Box 5).⁴⁵ According to the classification scheme of McKee et al., CTE begins focally, usually perivascularly at the depth of the sulci in the frontal cerebral cortex, and involves the superficial layers of the cerebral cortex. The pathology spreads slowly (over decades) to involve widespread regions of the medial cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem and spinal cord. Stages I and II are considered to be mild pathologies and are characterized by neurofibrillary tangles in focal epicenters of the frontal cortices. Stages III and IV represent severe forms of CTE, with more-widespread tau involvement. Notably, all seven cases of AD-associated CTE that were indentified in this study were stage IV, and no pure cases of AD existed in the cohort.45

Diagnosis

A diagnosis of CTE can be definitively ascertained only at autopsy. Clinical diagnosis of CTE can be problematic as the development of chronic neurological sequelae is not temporally related to a single concussive event and the symptoms typically manifest in later life after a period of latency.⁵⁶ Four categories of clinical criteria for CTE have been defined (Table 1).

To be classified as 'definite CTE' a case must present with neurological signs that are consistent with CTE and have pathological confirmation of tau deposition with or without deposition of amyloid or TAR DNA-binding protein 43 (TDP-43). Given the lack of established consensus criteria for the neuropathological classification of CTE, the two classification schemes described above^{45,51} can aid in diagnosis of definite CTE.

'Probable CTE' is defined as any neurological process involving two or more of the following clinical conditions: cognitive and/or behavioural impairment, cerebellar dysfunction, pyramidal tract disease and extrapyramidal disease. This syndrome has to be clinically distinguishable from other neurological disorders and must be consistent with the clinical description of CTE. Neuroimaging studies can provide evidence in support of probable CTE. Using ¹⁸F-FDDNP PET—a neuroimaging tool to measure tau and amyloid deposition in the brain—increased subcortical and cortical signals were detected in five retired National Football League players who exhibited cognitive and behavioural symptoms.⁵⁷ However, as ¹⁸F-FDDNP binds both fibrillary tau and amyloid, increased ¹⁸F-FDDNP signal cannot be solely attributed to tau, and additional histopathological confirmation is, therefore, needed. A negative amyloid PET scan could be useful in ruling out preclinical, prodromal or overt AD.58 Evidence of glucose hypometabolism on PET, or hypoperfusion on single-photon emission CT (SPECT), can also support a diagnosis of CTE (discussed below). Other neuroimaging findings that are supportive of probable CTE include nonspecific evidence of CNS trauma on structural imaging and/or DTI. In one case of a 50-year-old boxer with dementia and probable CTE, CSP presented as thinning and marked loss of fibre-tract integrity in the corpus collosum (Figure 2; B. D. Jordan, unpublished work).

The category of possible CTE involves brain pathology that cannot be reliably distinguished from other primary neurodegenerative disorders such as AD, frontotemporal dementia, vascular dementia, normal pressure hydrocephalus, multiple system atrophy, and Parkinson disease-related dementia. Cases of CTE and AD co-occurrence are well-documented⁴⁵ and, therefore, despite ancillary findings such as a positive amyloid PET scan, biparietal and/or bitemporal hypometabolism on glucose PET, elevated tau and/or decreased amyloid in the cerebrospinal fluid, co-existent CTE cannot be ruled out.

Any neurological process that is inconsistent with the clinical description of CTE and exhibits a pathophysiology unrelated to TBI would be classified as improbable CTE. Examples include brain tumours, stroke and inherited neurological disorders.

As biomarkers that reflect the natural history of CTE are currently nonexistent, characterization of preclinical and prodromal CTE (which are similar to the preclinical phases that have been documented in AD)⁵⁸ is premature. However, neuroimaging biomarker abnormities, which are indicative of axonal and myelin injury, have been observed in athletes who have been exposed to

Box 5 | McKee neuropathological classification of CTE⁴⁵

Stage I

Normal brain weight. Focal epicenters of perivascular p-tau, and neurofibrillary and astrocytic tangles involving the sulcal depths and typically affecting the superior and dorsolateral frontal cortices.

Stage II

Normal brain weight. Multiple epicenters at the depths of the sulci with localized spread from epicenters to the superficial layers of adjacent cortex. No neurofibrillary p-tau involvement in the medial temporal lobe.

Mild reduction in brain weight. Mild cerebral atrophy with dilatation of the lateral and third ventricles. Septal abnormalities. Moderate depigmentation of the locus coeruleus and mild depigmentation of the substantia nigra. Atrophy of the mammillary bodies and thalamus. Widespread p-tau pathology in the frontal, insular, temporal and parietal cortices. Neurofibrillary pathology in the amygdala, hippocampus and entorhinal cortex.

Stage IV

Marked reduction in brain weight with atrophy of the cerebral cortex. Marked atrophy of the medial temporal lobe, thalamus, hypothalamus and mammillary bodies. Severe p-tau pathology affecting most regions of the cerebral cortex and the medial temporal lobe, sparing the calcarine cortex. Severe p-tau pathology in the diencephalon, basal ganglia, brainstem and spinal cord. Marked axonal loss of subcortical white matter tracts.

Abbreviations: CTE, chronic traumatic encephalopathy; p-tau, phosphorylated tau.

Table 1 | Clinical criteria for chronic traumatic encephalopathy

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Classification	Definition	Clinical examples
Definite	Any neurological process consistent	Cognitive, behavioural, and/or

Delinite	with the clinical presentation of CTE along with pathological confirmation (tauopathy ± diffuse amyloid deposition ± TDP-43 deposition)	motor dysfunction
Probable	Any neurological process characterized by two or more of the following conditions: cognitive and/ or behavioural impairment; cerebellar dysfunction; pyramidal tract disease or extrapyramidal disease; clinically distinguishable from any known disease process and consistent with the clinical description of CTE	Cognitive impairment and extrapyramidal dysfunction suggestive of parkinsonism Associated cerebellar dysfunction that is inconsistent with parkinsonism
Possible	Any neurological process that is consistent with the clinical description of CTE but can be potentially explained by other known neurological disorders	Alzheimer disease or other primary dementia Parkinson disease Primary cerebellar degeneration Wernicke–Korsakoff syndrome Amyotrophic lateral sclerosis
Improbable	Any neurological process that is inconsistent with the clinical description of CTE and can be	Cerebrovascular disease Multiple sclerosis Brain neoplasm

Other inherited neurological

disorders

process unrelated to brain trauma Abbreviations: CTE, chronic traumatic encephalopathy; TDP-43, TAR DNA-binding protein 43.

explained by a pathophysiological

repetitive brain injury. For example, in studies of professional boxers, fractional anisotropy in the corpus collosum and internal capsule was lower compared with controls,59 and the apparent diffusion coefficient (ADC) was elevated in the cortical gray matter, and fractional anisotropy in deep white matter was decreased

Figure 2 | Brain imaging in a retired professional boxer with probable chronic traumatic encephalopathy. $\bf a$ | Axial T2-weighted brain MRI shows mild, diffuse volume loss, cavum septum pellucidum and cavum vergae. $\bf b$ | Saggital brain MRI demonstrates focal thinning and volume loss of the corpus collosum. $\bf c$ | Diffusion tensor imaging tractography reveals a focal defect and loss of white matter integrity in the corpus collosum.

compared with controls. 60 Similarly, trace radial diffusivity and axial diffusivity (purported measures of myelin and axonal pathology) increased among icehockey players over a season, with the damage involving regions of the corticospinal tract, the corpus collosum and the superior longitudinal fasiculus; however, no changes in fractional anisotropy were observed in this study. 61 Differences in white matter integrity have also been observed in athletes involved in soccer (a potentially high-impact sport) compared with those involved in swimming (a low-impact sport). 62

Abnormalities on PET and SPECT have also been reported in athletes with repetitive brain injuries. A unique pattern of glucose hypometabolism was detected in the posterior cingulate cortex, parieto-occipital lobes, frontal lobes and cerebellum of boxers. With the use of SPECT imaging, investigators have also observed brain hypoperfusion in the prefrontal and temporal poles, occipital lobes, anterior cingulate gyrus and cerebellum among active and retired professional American football players. 64

Pathophysiology

The pathophysiology of CTE is unknown, but is presumed to be a progressive tauopathy. 45,49 The mechanisms of phosophorylation, cell-to-cell propagation, and/ or oligomerization and misfolding of tau that result in the clinical phenotype of CTE remain to be elucidated. McKee and colleagues have postulated that repetitive brain trauma and deposition of hyperphosphorylated tau protein promote accumulation of other abnormally aggregated proteins including TDP-43, amyloid- β and α -synuclein. The frequency of progression from brain injury to clinical manifestation is, however, unknown, and factors that are reliably associated with progression have yet to be identified.

Chronic postconcussion syndrome

The term CPCS is used to describe an uncommon clinical phenomenon in which the athlete experiences post-concussive symptoms that do not seem to resolve, and often results in the athlete retiring from sport. In their 2011 study, King and Kirkwilliam use the term 'permanent PCS' to characterize a condition observed in

individuals from a nonathlete population who exhibited symptoms approximately 6.9 years after a concussion. A substantial proportion of individuals with permanent PCS (40–59%) experienced premorbid or postmorbid conditions such as depression, anxiety, post-traumatic stress, and/or pain, which were not directly attributable to the manifestations of concussion but could exacerbate the postconcussive symptoms. In this Review, CPCS is the preferred term as the clinical labelling of symptoms as 'permanent'—which suggests that they may never resolve—could be problematic. Although no unifying definition exists with regard to the duration of symptoms that is necessary to qualify an athlete as experiencing CPCS, for the following discussion CPCS is defined as postconcussive symptoms lasting longer than 1 year.

Epidemiology and symptoms

The exact frequency of CPCS among elite and nonelite athletes is unknown. In the general, nonsporting population, 10–15% of individuals are reported to remain symptomatic 1 year after concussion. ⁶⁶ Common symptoms of CPCS include headache, dizziness, impaired attention, poor memory, executive dysfunction, irritability and depression. Factors associated with CPCS include older age, premorbid and postmorbid anxiety and depression, and the severity of initial postconcussive symptoms. ⁶⁵

Investigations detailing the long-term consequences of a single sport-related concussion are scarce, which may be attributable to poor detection of such injuries owing to the transient nature and rapid recovery of post-concussive symptoms.⁶⁷ The majority of CPCS cases have been reported in the lay press⁶⁸ and, as such, lack scientific scrutiny.

In 1996, Kelly and Rosenberg described a classic case of CPCS in a retired professional football player who sustained multiple concussions over a long career and exhibited persistent symptoms that were consistent with a postconcussion syndrome.⁶⁸ Persistent visuospatial attention deficits have also been reported in players of the high-impact sport Australian Rules football at least 1 year after sustaining a concussion.⁶⁹ One study reported neurocognitive and neurophysiological changes in athletes who had sustained concussions more than 30 years earlier:⁶⁷ individuals who sustained a sports concussion performed particularly poorly on tests of episodic memory and response inhibition compared with athletes who had never experienced a concussion. Evidence of motor system dysfunction among the concussed athletes included delayed and attenuated evoked potentials on an auditory oddball paradigm, a prolonged cortical silence period (an assessment of motor cortex excitability that is measured using transcranial magnetic stimulation), and bradykinesia.

CPCS versus CTE

CPCS is a type of chronic TBI that is clinically distinct from CTE. Unlike CTE, CPCS has an acute onset that is temporally related to a single concussive event, and it does not present insidiously following a latent period—a defining characteristic of CTE.⁴⁵ Headache

is a prominent feature of CPCS but is not frequently encountered in CTE, with the exception of McKee stages I–II.⁴⁵ The pathological substrate of CPCS is unknown, and whether it involves the tau pathology that is classically recognized in CTE remains to be established. In addition, whether CPCS overlaps with CTE and/or represents McKee's neuropathological stages I and II⁴⁵ or Omalu's phenotype IV (incipient phenotype)⁵¹ has yet to be explored.

Conclusions

Acute and chronic TBI in sport represents an important public health concern in modern day society. Although brain injuries are not the most common type of sportrelated injury, they can be associated with substantial morbidity and, potentially, mortality. Concussions are often unrecognized and are, therefore, underreported. Accordingly, recognition of concussion through education and proper medical surveillance is of paramount importance. Failure to adequately manage concussion could result in persistent or chronic PCS or DCS. New neuroimaging techniques may be useful in assessment of both acute and chronic brain injury. DTI, it seems, might be of greater value for evaluation of chronic ultrastructural changes following repetitive brain injury than for assessment of acute concussion or the sequelae of a single mild concussion.

CPCS is a relatively uncommon condition among athletes that needs to be further elucidated to determine whether it is causally linked to CTE or represents a distinct comorbid condition. The neuropathological substrate of CPCS in athletes is unknown and warrants further investigation.

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The fact that antemortem diagnosis of CTE is difficult and that this syndrome can mimic other primary neurodegenerative disorders and has an insidious onset (typically manifesting only after an athlete has retired from sport) is of major concern. The exact frequency of CTE in athletes is unknown and, to date, the strongest putative risk factors for CTE are increased exposure to injury and older age. No reliable biomarkers currently exist to effectively diagnose CTE and monitor disease progression. At present, a definitive diagnosis of CTE can only be ascertained at autopsy, and the clinical diagnosis of CTE can only be 'probable' or 'possible'. Future advances in neuroimaging will hopefully assist in the diagnosis of this complex disorder, and in vivo documentation of tau deposition in the brain could potentially be used to identify athletes with a progressive tauopathy as a result of repetitive sports-related TBI.

Review criteria

Articles were obtained through reference-list searches, cited reference searches, and regular review of sports medicine, brain injury, rehabilitation, neurotrauma, neurological and neurosurgery journals. A PubMed biomedical literature search using the key words "sports concussion", "sports-related traumatic brain injury", "chronic traumatic encephalopathy", "chronic traumatic brain injury", "second-impact syndrome", "malignant cerebral oedema", "diffuse cerebral swelling", "postconcussion syndrome", "dementia pugilistica", and "punch-drunk syndrome" was also performed. Articles included full-text papers and abstracts written in English as well as book chapters and texts. There were no restrictions on the dates of the publications.

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EXHIBIT 7

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Review Article

Chronic Traumatic Encephalopathy: A Review

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Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease that is a long-term consequence of single or repetitive closed head injuries for which there is no treatment and no definitive pre-mortem diagnosis. It has been closely tied to athletes who participate in contact sports like boxing, American football, soccer, professional wrestling and hockey. Risk factors include head trauma, presence of ApoE3 or ApoE4 allele, military service, and old age. It is histologically identified by the presence of tau-immunoreactive NFTs and NTs with some cases having a TDP-43 proteinopathy or beta-amyloid plaques. It has an insidious clinical presentation that begins with cognitive and emotional disturbances and can progress to Parkinsonian symptoms. The exact mechanism for CTE has not been precisely defined however, research suggest it is due to an ongoing metabolic and immunologic cascade called immunoexcitiotoxicity. Prevention and education are currently the most compelling way to combat CTE and will be an emphasis of both physicians and athletes. Further research is needed to aid in pre-mortem diagnosis, therapies, and support for individuals and their families living with CTE.

1. Introduction

Chronic traumatic encephalopathy (CTE) has been defined as a progressive neurodegenerative disease caused by repetitive head trauma [1]. CTE was first described in 1928 when Dr. Harrison Martland, a New Jersey medical examiner, began to note a constellation of symptoms in boxers. In an article he published in the Journal of the American Medical Association entitled Punch Drunk, he describes the boxers, "cuckoo," "goofy," "cutting paper dolls," or "slug nutty" [2]. Punch drunk was later termed dementia pugilistica, literally meaning dementia of a fighter. However, with the evolution of sports like American football, these symptoms were also being reported in athletes other than boxers and was renamed chronic traumatic encephalopathy in the 1960s

CTE has become a popular topic due to its close association with American football, hockey, soccer, boxing, and professional wrestling. Many of these affected athletes, mostly retired, have struggled in their later years with depression, substance abuse, anger, memory/motor disturbances, and suicide [3]. Autopsy results from these athletes

have suggested a link between these emotional, cognitive, and physical manifestations and CTE [3–5]. In addition to athletes, military soldiers have become another group of interest as many are returning from the battlefield with brain injuries from blast trauma causing closed head injury. In this paper we present a summary of the epidemiology, risk factors, clinical presentation, pathophysiology, neuropathological findings, treatment/prevention, and future research pertaining to CTE.

2. Epidemiology

Concussion or mild traumatic brain injury (mTBI) is one of the most common neurologic disorders accounting for approximately 90% of all brain injuries sustained [4]. Such injuries are a common occurrence in athletes with an estimated 1.6–3.8 million sport-related concussion annually in the USA [5]. This can be seen as a gross underrepresentation of the true number as many athletes do not seek medical attention or vocalize their symptoms. This may be due to head trauma being regarded as benign, or in some the injury

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is not recognized at all. These behaviors are driven by the athletes' desire to return to play and the pressure to perform [6]. DeKosky et al. reported that each year more than 1.5 million Americans have mTBI with no loss of consciousness and no need for hospitalization as well as an equal number with conscious impairing trauma but insufficiently severe to require long-term hospitalization [7].

In a 2009 review of CTE, McKee et al. found that of 51 neuropathologically diagnosed cases of CTE 46 (90%) occurred in athletes. Specifically, athletes participating in American football, boxing, soccer, and hockey comprise the majority of cases. Many of these athletes began their respective sports at a young age between 11 and 19 years [5]. While it is not clear at what age CTE can begin, McKee has neuropathologically diagnosed CTE changes in asymptomatic 18-year-old high school football player with a history of concussion. While the exact incidence of CTE is unknown, it is thought to vary widely based on sport, position, length of career, number of head injuries, age of first head injury, and genetics [8].

3. Risk Factors

It has been well established that repetitive concussive or subconcussive blows to the head place individuals at risk for CTE [5, 6, 8]. CTE has been associated with athletes who participate in contact sports like American football, boxing, hockey, soccer, and professional wrestling. Other sports that are not directly associated with CTE, but have well-documented cases of concussion, include mixed martial arts, rugby, and horseback riding. Other groups at risk for repetitive head trauma and CTE are military veterans, epileptics, and victims of domestic abuse [5]. It has been reported that approximately 17% of professional retired boxers will exhibit CTE [3]. Although each group listed has a unifying factor of head trauma, they differ in particular aspects that may influence the severity or chronicity of their injury (see Table 1 for a summary of risk factors).

A recent study by Crisco et al. examined head impact exposure in collegiate football players and found that the average number of impacts received by an individual player during a single season was 420 with a maximum of 2,492 [9]. These impacts vary in severity based on their position. Offensive linemen, defensive linemen, and linebackers had the most frequent impacts while quarterbacks and running backs received the greatest magnitude of head impacts [9]. In the literature McKee and colleagues reported that in five football players with diagnosed CTE all played similar positions: 3 were offensive linemen, 1 defensive linemen, and one linebacker [5]. However, according to Boston University's Center for the Study of Chronic Traumatic Encephalopathy, CTE has also been found in other position players like safety and wide receiver dismissing the idea that only certain positions are at risk for developing CTE.

While it is clear that anyone who suffers repeated head trauma, regardless of the mechanism, may carry the risk of developing CTE, there is no clear consensus on how much or how little trauma is needed to cause CTE. While most feel

Table 1: Risk factors associated with chronic traumatic encephalopathy.

- (i) Head trauma: single or repetitive
- (ii) History of head concussion
- (iii) Participation in the following

Boxing

American football: offensive/defensive linemen/linebackers/running backs

Soccei

Professional wrestling

Hockey

Military service: blast injuries

- (iv) Length of sport participation
- (v) Epileptics
- (vi) Victims of domestic abuse
- (vii) Age of injuries: younger ages and older ages
- (viii) Genetic variation: ApoE3 or ApoE4

CTE is a manifestation of repetitive trauma, the question still stands if it can be caused by a single TBI [10]. In a study by Johnson et al., widespread tau and beta-amyloid deposition was found in the brains of individuals who suffered a single traumatic brain injury. The study included the examination of postmortem brains from long-term survivors (1–47 years) of a single TBI (N = 39) versus uninjured age-matched controls (N = 47). Results showed NFTs to be exceptionally rare in young uninjured controls, yet were abundant and diffuse in one-third of TBI cases. This was also true of beta-amyloid deposition, which was found in greater density following TBI than controls [11]. While these brains showed classic changes associated with CTE, they did not have the symptomatic profile to accompany their neuropathologic findings [11]. If these subjects went on to have repeated brain injury, it would be reasonable to expect more extensive damage with more pronounced clinical symptoms.

In a study of repeated head trauma in mice, Kane et al. created an animal model where mice did not suffer severe TBI but rather mTBI to look for CTE-like changes. They reported that exposure to head trauma for 5 consecutive days showed increased expression of glial fibrillary acidic protein and phospho-tau 30 days (~160% increase) after the last injury when compared to controls. They also reported that with their mTBI model they did not find edema, cortical contusions, obvious loss of neuronal matter beneath the skull, disruption of the blood brain barrier, or microglial activation. However, they compared this to mice that were subject to a single traumatic injury and found substantial microglial activation in the hippocampus and overlying cortex 30 days after the initial impact [12].

Another high-risk group that has recently been studied are individuals in the military [12]. Operations in Iraq and Afghanistan are reporting that TBI accounts for roughly 28% of all combat casualties and approximately 88% of these are closed-head injuries [12]. While these numbers are significant, the US Defense and Veterans Brain Injury

Center has estimated that approximately 180,000 soldiers have been diagnosed with mTBI between 2001 and 2010 while others estimate the number to be more than 300,000. Additionally, soldiers may also be exposed to toxins like organophosphates, chemical nerve agents, and heavy metals like uranium increasing their risk for brain injury [13].

Age is another possible risk factor for the development of CTE. At younger ages, while the brain is developing traumatic injury may begin the cascade of destructive events and compounded through the years of continued play. Conversely, at younger ages the brain has more plasticity allowing greater ability to manage injury than that in the mature brain [8, 10]. Length of play is another risk factor where longer careers with prolonged exposures to injury may cause more severe CTE. Of the 51 cases reviewed by Dr. McKee, 39 boxers had an average career of 14.4 years (range 4–25) while the 5 football players averaged careers of 18.4 years (range 14–23 years). These athletes began their respective sports between 11 and 19 years of age [5].

Genetic factors have also been thought to play a role in the development of CTE specifically the apolipoprotein E gene (ApoE). The ApoE4 allele has been well described in its association with Alzheimer's disease (AD) where individuals with homozygous ApoE4/E4 genotype have a 19fold increased risk of developing AD [14]. This same gene is now thought to possibly have a role in the development of CTE [5]. Studies have shown that ApoE4-positive individuals had poorer outcomes with head trauma. Teasdale et al. reported that that patients with ApoE4 allele are more than twice as likely than those without ApoE4 to have unfavorable outcomes 6 months after head injury [15]. Kutner et al. examined 53 professional American football players to see if their cognitive functioning differed based on age and ApoE4 genotype. They reported that older age and presence of ApoE4 scored lower on cognitive tests than did those without the allele or with less playing experience [16]. Jordan et al. looked at ApoE4 genotype in boxers in relation to chronic TBI. They found that all boxers with severe impairment, based on the chronic brain injury scale, had at least 1 ApoE4 allele. Therefore, they reported that ApoE4 may be associated with increased severity of chronic neurologic deficits in highexposure boxers [17].

In McKee and colleagues' review of the 51 CTE cases, ApoE genotyping was reported in 10 cases where 50% carried at least one ApoE4 allele and one was homozygous for E4. While they did not report what the other 4 genotypes were, it raised their suspicions to believe that ApoE4 was the gene of interest. In animal studies ApoE4 transgenic mice had greater mortality from TBI than those with ApoE3 allele. Another study showed that transgenic mice that overexpress ApoE4 allele showed increased deposition of beta-amyloid after experimental TBI [5].

However, a study by Omalu et al. reported that 70% of their CTE cohort had the ApoE3 genotype. Of the 17 athletes they used in their study they were able to determine the ApoE genotype in 10 of 14 professional athletes and in 2 of 3 high school athletes. Of the 10 professional athletes 90% had at least one ApoE3 allele, and 7 of the 10 with confirmed ApoE genotype also had CTE. Of these 7 athletes with CTE 100%

had at least one ApoE3 allele (5 E3/E3, 2 E3/E4). It should also be noted that the only professional athlete in their study that did not have the E3 allele (E2/E4) was negative for CTE. Additionally, the two other professional athletes that had the ApoE allele but did not have CTE were E2/E3 (24 years old) and E3/E3. The authors note that the one case of E3/E3 that did not have tauopathy was assessed from only select sections of the brain as they did not have access to the full brain. Of the two high school athletes both were E3/E3 genotypes and did not show any histological signs of CTE [18].

4. Clinical Presentation

It is important to define the timeline of CTE symptom development to distinguish it from concussive or postconcussive syndrome (PCS). The symptoms associated with acute concussion are headache, blurred vision, amnesia, tinnitus, fatigue, and slurred speech with resolution within days to weeks if managed properly. Although there is no strict timeline to the acute injury phase, it has typically been reported as three months, but 80-90% of patients show full recovery within the first 10 days [19]. When symptoms extend beyond three months, the individual is said to have PCS. These individuals will have additional symptoms of physical, emotional, cognitive, and behavioral problems [6]. PCS also has a variable timeline where symptoms typically improve within one year but may in some cases require several years for resolution. For those with persisting or permanent PCS symptoms, they would logically be considered to have CTE.

However, the typical clinical course of an individual who develops CTE is not as linear as direct progression from concussion to PCS to CTE. The onset of CTE symptoms typically starts later in the lives of certain athletes after the individual has removed themselves from competition. As reported by McKee, the first symptoms of CTE were noted at ages ranging from 25 to 76 years. McKee also reported that at the time of retirement one-third of these athletes were symptomatic with another half becoming symptomatic within 4 years of leaving sports [5]. In 14 cases (30%), mood disturbances were reported while movement abnormalities like Parkinsonism, ataxia, antalgic gait, and dysarthric speech were reported in 41% of subjects [5]. The course of symptom progression seems to follow a somewhat continuous path beginning with cognitive and emotional decline leading to eventual motor deterioration [5].

Initially, patients begin to have poor concentration, attention, and memory along with disorientation, dizziness, and headaches. They typically progress to experience irritability, outbursts of violent or aggressive behavior, confusion, and speech abnormalities. During this stage of the disease, there is a high frequency of suicide, drug overdose, and mood disorders, mainly major depressive disorder [5]. A study by Omalu and colleagues describes a similar clinical profile with a latent asymptomatic period between play and symptom onset. He reports worsening of cognitive and social functioning leading to poor money management, bankruptcy, social phobias, paranoid ideation,

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insomnia, poor relationships, divorce, emotional/physical abuse, and substance abuse [18]. Family and friends of the affected individuals reported many of these symptoms to researchers through standard forensic interviews [18].

As the disease progresses in severity, there is a greater loss of motor functioning. Some patients may develop Parkinsonian symptoms of tremors, masked facieses, wide propulsive gait, poor speech, ocular abnormalities, vertigo, bradykinesia, deafness, and a small group developing dementia. Currently, the number of cases with confirmed dementia remains small. As more postmortem exams are done in the at risk group, it is expected more cases will be diagnosed. Some individuals with CTE have committed suicide, overdosed on drugs, or died from accidents preventing progression of the disease [5, 20].

5. Pathophysiology

The development of CTE is due to repetitive traumatic brain injury from the acceleration/deceleration forces of closed head impacts [5]. Damage to the brain generally occurs when the brain collides against the skull causing damage to the same side as the collision, coup, or to the opposite side of the impact, countercoup [6]. High-speed decelerations may also cause mechanical and chemical injury to the long axons resulting in traumatic/diffuse axonal injury. Crisco et al. report that impacts to the top of the head had the lowest rotational force but highest linear force leading more to cervical spine injuries. However, lateral blows cause rotational forces, which are the typical cause of mild traumatic brain injury [6]. While there is a firm understanding of head trauma being the general cause of the brain damage in CTE, researchers have not agreed upon a unifying mechanism of injury. Originally the associated axonal damage was thought to be due to shearing or mechanical forces at the time of injury. However, it is now reported that axonal shearing or tearing is a secondary event to the acute inflammation and neurodegeneration of axons [5]. In the acute setting there is rapid axonal swelling, perisomatic axotomy, and Wallerian degeneration [5].

Gavett et al. offered a general description of how the damage may occur through the repeated traumatic injury of axons. Damage to axons would cause changes in membrane permeability and ionic shifts causing a large influx of calcium. Subsequent release of caspases and calpains would trigger tau phosphorylation, misfolding, shortening, and aggregation as well as cytoskeleton failure with dissolution of neurofilaments and microtubules [8].

This idea was elaborated on in a recent paper by Blaylock and Maroon who describes the concept of immunoexcitotoxicity as a possible central mechanism for CTE. He describes a cascade of events that begin with an initial head trauma, which "primes" the microglia for subsequent injuries. When the homeostasis of the brain is disturbed, some of the microglia undergo changes to set them in a partially activated state. When these microglia become fully activated by continued head trauma, they release toxic

levels of cytokines, chemokines, immune mediators, and excitotoxins like glutamate, aspartate, and quinolinic acid. These excitotoxins inhibit phosphatases, which results in hyperphosphorylated tau and eventually neurotubule dysfunction and neurofibrillary tangle deposition in particular areas of the brain [10]. There is also an apparent synergy between the proinflammatory cytokines and glutamate receptors that worsen neurodegeneration in injured brain tissue. This combination also increases the reactive oxygen and nitrogen intermediates that interfere with glutamate clearance keeping the injury response high. Priming can also occur from insults to the brain like systemic infections, environmental toxins, and latent viral infections in the brain (cytomegalovirus and herpes simplex virus) [10].

The microglia, however, have a dual function allowing them to switch between being neurodestructive and neuroreparative. During acute injury the microglia are responsible for containing the damage with inflammation, cleaning up debris, and repairing the surrounding damaged tissue [10]. However, if the individual experiences a second brain trauma or multiple continuous traumas, the microglia may never have the chance to switch from proinflammatory to reparative mode [10]. Such repetitive trauma may place the brain in a state of continuous hyperreactivity leading to progressive and prolonged neuronal injury. This would support the evidence that repeated mTBI results in a higher incidence of prolonged neurological damage than single-event injury [10].

The eventual neurodegeneration is also dependent on other factors like the age of the brain at the time of injury. Several studies have shown that older individuals have poorer outcomes when compared to younger subjects experiencing TBI. Streit et al. showed that as the microglia age, they become more dysfunctional, which may impair their ability to terminate immune activation. Therefore, as the brain grows older, it has more activation of microglia with weaker mitochondrial functioning, neuronal and glial dystrophy, higher levels of inflammation, and lifetime exposures to environmental toxins [10].

6. Gross Pathology Findings

As described by Corsellis et al., the most common gross pathological findings in CTE included reduced brain weight, enlargement of the lateral and third ventricles, thinning of the corpus callosum, cavum septum peallucidum with fenestrations, scarring, and neuronal loss of the cerebellar tonsils. Brain atrophy was most severe in the frontal lobes (36%), temporal lobes (31%), and parietal lobes (22%) with the occipital lobe rarely being affected [5]. McKee and colleagues reported that with increasing severity of disease marked atrophy is noted in the hippocampus, entorhinal cortex, and the amygdala [5]. Blaylock and Maroon reported that these areas showed the most severe atrophy and were noted to have the highest concentration of glutamate receptors and cytokine receptors [10].

7. Microscopic Pathology

According to Dr. Bennet Omalu, a forensic neuropathologist, the basic feature of CTE is the presence of sparse, moderate, or frequent band-shaped, flame-shaped small globose and large globose neurofibrillary tangles (NFTs) in the brain accompanied by sparse, moderate, or frequent neuropil threads (NTs) [18]. Similarly, McKee and colleagues described the core pathology of CTE to include tau-reactive NFTs, astrocytic tangles, and dot-like spindle-shaped NTs [10]. These changes are commonly noted in the dorsolateral frontal, subcallosal, insular, temporal, dorsolateral parietal, and inferior occipital cortices. Additionally, Dr. McKee also reported occasional tau immunoreactive neuritis and NFTs in the posterior, lateral, and/or anterior horns of the spinal cord (see Table 2) [10].

Beta-amyloid ($A\beta$) deposition is an inconsistent finding in CTE as Dr. McKee noted that of the 51 cases of confirmed CTE she reviewed that only 3 (6%) had amyloid angiopathy [5]. Animal studies by Iwata et al. used swine TBI models to show minimal $A\beta$ accumulation in axons acutely after injury but saw greater accumulation one month following injury [20]. Similarly Chen et al., also using a swine TBI model, found evidence of axonal pathology 6 months following rotational brain injuries [21].

Although CTE and Alzheimer's disease (AD) both have NFTs and possibly beta-amyloid plaques, there are several unique features that distinguish the two [8]. First, betaamyloid deposits are only found in 40% to 45% of patients with CTE while they are present in nearly all cases of AD. Secondly, the tau distribution in CTE is located more in the superficial cortical laminae whereas in AD they are found in large projection neurons in deeper layers. It is also important to note is the distribution of the NFTs in CTE that extremely irregular with uneven foci in the frontal temporal and insular cortices, while AD has a more uniform cortical NFT distribution. DeKosky et al. noted that the hippocampus is frequently spared by tauopathy in CTE, whereas it is the first location affected by tauopathy in AD [7]. Lastly, NFTs in CTE are most concentrated at the depths of the cortical sulci and are typically perivascular, which might indicate that there are disruptions of cerebral microvasculature and the blood-brain barrier at the time of injury leading to NFT formation [8].

A recent study by Omalu et al. described four histomorphologic phenotypes of CTE in American athletes (see Table 3). They examined specimens from 17 deceased athletes, 10 of which had histopathologically confirmed CTE. All were male, age range of 17–52, (8 were American football players, 4 professional wrestlers, 1 mixed martial arts fighter, 1 professional boxer, and 3 high school American football players). Omalu and colleagues created these histologic phenotypes based on the presences or absence of NFTs, NTs, and diffuse amyloid plaques as well as their quantitative distribution in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, and cerebellum. These results are summarized in Tables 1 and 2. Phenotype one shows sparse to frequent NFT and NTs in the cerebral cortex and brainstem without involvement of the subcortical nuclei, basal ganglia, or cerebellum without any beta-amyloid.

TABLE 2: Areas of damage in the brain.

Gross areas of damage

- (i) Reduced brain weight with atrophy of
 - Frontal lobe
 - Temporal lobe
 - Parietal lobe
 - Occipital lobe
- (ii) Enlargement of lateral and third ventricles
- (iii) Thinning of the corpus callosum
- (iv) Cavum septum pellucidum with fenestrations
- (v) Scarring and neuronal loss of cerebellar tonsils
- (vi) Pallor of substantia nigra

Areas of tau NFTs and NT

- (i) Superficial cortical layers
- (ii) Dorsolateral frontal
- (iii) Subcallosal
- (iv) Insular
- (v) Temporal
- (vi) Dorsolateral parietal
- (vii) Inferior occipital cortices
- (viii) Thalamus
- (ix) Hypothalamus
- (x) Substantia nigra
- (xi) Olfactory bulbs
- (xii) Hippocampus
- (xiii) Entorhinal cortex
- (xiv) Amygdala
- (xv) Brainstem

Phenotype two is the same as the first except they show diffuse beta-amyloid plaques. The third group had higher concentrations of NFTs and NTs only in the brainstem without involvement elsewhere with no beta-amyloid. The fourth group had sparse NFTs and NTs in the cerebral cortex, brainstem, subcortical nuclei, and basal ganglia with an unaffected cerebellum and no beta-amyloid [18].

Trans-activator regulatory DNA-binding protein 43 or TDP-43 has been a recent addition to the growing neuropathologic findings associated with CTE. TDP-43 is a highly conserved protein that is found in many tissues including the CNS [22]. It plays a significant role in mediating the response of the neuronal cytoskeleton to axonal injury [8]. In a study by McKee et al., they reported widespread TDP-43 proteinopathy in 80% of their CTE cases. Until this study, TDP-43 was thought to be a unique finding to amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP) but has now been found in other neurodegenerative diseases as a secondary pathology [22].

TABLE 3: Emerging histomorphologic phenotypes in American athletes.

Phenotype	Histological findings
1	Sparse to frequent NFT and NTs in the cerebral cortex and brainstem without involvement of the subcortical nuclei, basal ganglia, or cerebellum without any beta-amyloid
2	Sparse to frequent NFT and NTs in the cerebral cortex and brainstem with diffuse beta-amyloid deposition. No involvement of the subcortical nuclei, basal ganglia, or cerebellum
3	Higher concentrations of NFTs and NTs only in the brainstem. No involvement elsewhere or any beta-amyloid
4	Sparse NFTs and NTs in the cerebral cortex, brainstem, subcortical nuclei, and basal ganglia with an unaffected cerebellum and no beta-amyloid [18]

8. Clinicopathologic Correlations

The typical symptoms of CTE can be directly connected to the specific areas of the brain that are injured during the progression of disease. Based on these symptoms it is clear that there is damage to the hippocampal-septohypothalamic-mesencephalic circuitry (Papez circuit) also known as the emotional or visceral brain [5]. Damage to these areas correlate to the behavioral symptoms of emotional liability, aggression, and violence. Damage to the hippocampus, enteorhinal cortex, and medial thalamus conceivably causes the commonly reported complaint of memory disturbance. Destruction to the frontal cortex and white matter may result in the dysexecutive symptoms found throughout the many cases of CTE. Motor abnormalities may be due to degeneration of the substantia nigra and pars compacta along with symptoms of dysarthria, dysphagia, and ocular malfunction due to brainstem nuclei injury like the hypoglossal and oculomotor nuclei (see Table 4) [5].

9. Neurological Sequelae

Historically amyotrophic lateral sclerosis (ALS) has been thought to be a sporadic disease with no single causative factor. Literature has reported risk factors to include trauma to the brain or spinal cord, strenuous physical activity, exposure to heavy metals, cigarette smoking, radiation, electrical shocks, and pesticides [22]. Given these risk factors, the literature strongly correlates a history of head trauma with increased incidence of ALS. In a case control study, Chen et al. reported that having repeated head trauma within the 10 years prior to diagnosis had a 3-fold higher risk of ALS [23]. The same group also did a meta-analysis of 8 ALS studies and estimated a pooled odds ratio of 1.7 (95% CI: 1.3, 2.2) for at least one previous head injury. Another study reported increased ALS incidence and mortality in professional Italian soccer players when compared to the general population [24]. Additionally, an incidence study of 7,325 Italian professional soccer players showed an ALS incidence 6.5 times higher than expected [25]. ALS has also been seen in higher numbers among American and Canadian football players when compared to the general population [22]. The risk of ALS has also been reportedly high in war veterans. A study of Gulf War veterans reported that the risk of ALS was increased 2-fold during the 10 years following service [26]. A study by Schmidt et al. reported that veterans who received head trauma during war had an adjusted odds

ratio for the development of ALS of 2.33 (95% CI: 1.18–4.61) [27].

A recent study by McKee and colleagues examined and compared the brains and spinal cords of 12 athletes with confirmed CTE to 12 cases of sporadic ALS to 12-age matched controls. Of the 12 CTE cases, 3 also had a diagnosed motor neuron disease (MND) resembling ALS. The study found that those with CTE and the motor neuron disease not only had the typical neuropathologic presentation of CTE with tau-NFT, NT, and TDP-43 throughout the brain and brain stem, but they also had these changes in the anterior horns of the spinal cord in high concentrations. Of the 9 CTE patients that did not have the MND, they had similar CTE neuropathology, but it did not affect the spinal cord as significantly. When compared to the samples of sporadic ALS, they found TDP-43 immunoreactivity in all 12 cases with no tau immunoreactive NFTs. The agematched controls showed no TDP-43 or tau reactivity. These results indicate that the widespread tauopathy and TDP-43 proteinopathy of CTE can in some cases extend beyond the brain and the brain stem to severely affect the spinal cord. The authors have labeled these cases as having chronic traumatic encephalomyelopathy (CTEM). While this has only been identified in three cases, it opens the floor to further discussion and research to see if CTEM is in fact a unique disease or just the coincidental occurrence of ALS and CTE. McKee has stated that the tau pathology in the three cases of CTEM is not only distinct from that of sporadic ALS, but the nature and distribution of the TDP-43 proteinopathy are also unique [22].

10. Diagnosis

Currently the only way to definitively diagnose CTE is through postmortem neuropathological autopsy [8]. Clinical diagnosis is difficult due to a lack of consensus on diagnostic criteria or large-scale longitudinal clinicopathologic correlation studies [8]. The differential diagnosis for CTE usually includes diseases like AD and frontotemporal dementia (FTD), which all share similar clinical symptoms, and all may have a history of head trauma making a clinical diagnosis difficult. Although age can help in distinguishing between AD and CTE, it does not help when deciding between FTD and CTE.

It is the hope of many that the advances in neuroimaging will aid in detecting chronic and acute changes associated with CTE. Diffusion tensor imaging (DTI) has been reported

Table 4: Clinicopathological correlations [5].

Damage area	Clinical presentation	
Hippocampus Entorhinal cortex Medial thalamus	Early deficits in memory	
Frontal cortex and underlying white matter	Dysexecutive symptoms	
Dorsolateral parietal Posterior temporal Occipital cortices	Visuospatial difficulties	
Substantia nigra Pars compacta	Parkinsonian motor features	
Cortical and subcortical frontal damage Cerebellar tract injury in brainstem	Gait disorder: staggered, slowed, ataxic	
Brainstem nuclei (hypoglossal/oculomotor)	Dysarthria, dysphagia, ocular abnormalities	
Amygdala	Aggression and violent outbursts	

to be sensitive enough to assess axonal integrity in the setting of mild, moderate, and severe TBI. DTI studies have shown their ability to show occult white matter damage after mTBI that was not visible on typical MRI scans. A study by Kumar et al. tracked serial changes in white matter using DTI techniques in mTBI and found that fractional anisotropy (FA) and mean diffusivity (MD) in the genu of the corpus callosum appear early and persisted at 6 months as a secondary injury to microgliosis [28]. Another study by Inglese et al. showed the abilities of DTI as they reported significant abnormalities in various regions of the brain after mTBI when compared to controls [29]. A third study by Henry and colleagues used DTI to detect changes in white matter by comparing a group of 10 nonconcussed athletes to 18 concussed athletes. They reported that at 1-6 days and at 6 months following concussion there was FA in dorsal regions of both cortical spinal tracts and the corpus callosum [30].

Although researchers are trying to identify biomarkers to aid in diagnosis, there currently are no makers identified in the literature that can be used to diagnosis CTE. However, there are several that are believed to help in identifying CTE like the use of magnetic resonance spectroscopy that can detect changes in glutamate/glutamine, N-acetyl aspartate, and mylo-inositol which have been shown to be abnormal in brain injury [8]. There has also been discussion of attempting to measure tau and phospho-tau in the cerebrospinal fluid of those suspected of having CTE [8].

11. Treatments/Prevention

Currently, the treatment methodologies for CTE are purely preventive. However, in sports like American football, prevention of head trauma is a seemingly difficult goal to attain. Hard hits and head collisions are more than simple aspects of the game; they are part of the sports identity. Therefore, prevention would require a multifaceted approach involving

administrators, coaches, players, referees, team physicians, and even the fans who watch the games. The administrators create the policies that penalize athletes for reckless or dangerous hits as well as setting equipment standards for the various leagues. It is the role of the coaches to teach their players correct and safe technique for tackling, hitting, and personal protection while creating a team culture that encourages hard but controlled play. Coaches also need to be aware of the cumulative effect of repetitive mTBI and limit the amount of full contact during practice and drills. It is the role of the players to understand the potential dangers and consequences of head trauma beyond their playing years so they can protect themselves and limit the number of injuries during their career. It is also incumbent on the athlete to not downplay their injuries and to seek help or advice if they are suffering from signs or symptoms of head trauma. As for the referees, it is their role to create a safe playing environment and uphold the rules set forth to protect the players whether on the field, in the ring, or on the ice. As for the team physician, it is their task to remove players from play and appropriately manage their mTBI until they meet the return-to-play criteria. The decision to clear a player is challenging for the physician who has no baseline information of the player's cognitive function prior to the injury. Therefore, it has been suggested that players undergo neuropsychological testing prior to participation in sports as a tool to properly assess the athlete's cognitive deficits both acutely and chronically.

Another aspect of prevention is improving the protective equipment worn by the athletes. It has been shown that helmets and mouth guards function very well in protecting the player from severe head injury if the helmet fits correctly, is strapped in place, and lined with the appropriate padding [6]. A study by Viano and Halstead compared American football helmets from 1970 to 2010 and reported that the newer helmets are heavier, primarily from more padding, longer, higher, and wider then their 1970s counterparts. These larger helmets were better at absorbing forces and impacts associated with concussions in American football [31]. While helmets are important, they may also give some players a false sense of protection leading to a more reckless and violent style of play. Neck strength is another factor that can be important in minimizing head injury especially in younger populations of athletes and should be emphasized by trainers and strength coaches [6]. Some groups are looking for medical therapies to limit the damage after a head injury. Particularly, the use of beta-amyloid-lowering medications has been shown to improve the outcomes following TBI in rodent models [7].

12. Future Considerations for Research

Although there has been an exponential growth in research and interest in CTE over the last five years, the full understanding of it still remains in its infancy. Affected athletes have been the greatest supporters as Boston University's Center for the Study of CTE has more than 260 former athletes in their brain and spinal cord donation registry.

These donations will supply researchers with a wealth of information that will improve animal models, better define the mechanism of injury, as well as advance diagnosis and treatment. As the foundation of knowledge grows, we can better identify genetic variants that put individuals at risk for CTE. The CTE community will also benefit from ongoing concussion research as groups look for acute biomarkers to be used as a diagnostic test for brain injury. There is also a need for further research regarding the role of advanced neuroimaging like DTI and its ability to possibly detect early signs of acute injury. Additionally, more work must be done to quantify the magnitude and frequency of head impact that is needed to cause the neurodegeneration associated with CTE.

13. Conclusions

Chronic traumatic encephalopathy is a neurodegenerative disease that is a long-term consequence of single or repetitive closed head injuries for which there is no treatment and no definitive premortem diagnosis. It has been closely tied to athletes who participate in contact sports like boxing, American football, soccer, professional wrestling, and hockey. Aside from repeated head trauma, risk factors include presence of ApoE3 or ApoE4 allele, military service, and old age. It is histologically identified by the presence of tau-immunoreactive NFTs and NTs with some cases having a TDP-43 proteinopathy or beta-amyloid plaques. It has an insidious clinical presentation that begins with cognitive and emotional disturbances and can progress to Parkinsonian symptoms. The exact mechanism for CTE has not been precisely defined; however, research suggests it is due to an ongoing metabolic and immunologic cascade called immunoexcitotoxicity. Current research is attempting to identify specific biomarkers along with more sophisticated imaging techniques for the diagnosis of CTE. Future research should also be centered around how to manage CTE as suicide is a common fate for those battling the disease. Further efforts need to be made to educate players, coaches, and administrators of all levels of athletics to make them aware of the determents of mTBI and how to best protect themselves. There must also be further investigations into the possible link between CTE and motor neuron disease. Establishing such a causal link may open new doors in ALS research and hopefully lead to better treatments. Through the continued efforts of athletes, scientists, and physicians, our knowledge of CTE will advance and allow for the evolution of better diagnosis, treatment, and prevention.

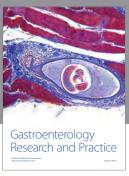
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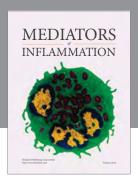
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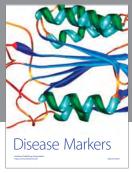
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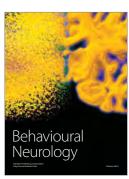


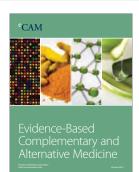




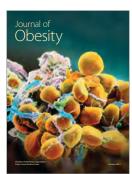


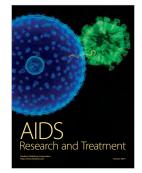


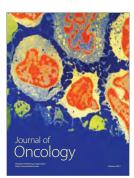












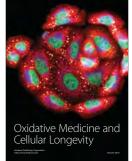


EXHIBIT 8

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CASE REPORT

Tauopathy PET and amyloid PET in the diagnosis of chronic traumatic encephalopathies: studies of a retired NFL player and of a man with FTD and a severe head injury

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Single, severe traumatic brain injury (TBI) which elevates CNS amyloid, increases the risk of Alzheimer's disease (AD); while repetitive concussive and subconcussive events as observed in athletes and military personnel, may increase the risk of chronic traumatic encephalopathy (CTE). We describe two clinical cases, one with a history of multiple concussions during a career in the National Football League (NFL) and the second with frontotemporal dementia and a single, severe TBI. Both patients presented with cognitive decline and underwent [¹⁸F]-Florbetapir positron emission tomography (PET) imaging for amyloid plaques; the retired NFL player also underwent [18F]-T807 PET imaging, a new ligand binding to tau, the main constituent of neurofibrillary tangles (NFT). Case 1, the former NFL player, was 71 years old when he presented with memory impairment and a clinical profile highly similar to AD. [18F]-Florbetapir PET imaging was negative, essentially excluding AD as a diagnosis. CTE was suspected clinically, and $[^{18}F]$ -T807 PET imaging revealed striatal and nigral $[^{18}F]$ -T807 retention consistent with the presence of tauopathy. Case 2 was a 56year-old man with personality changes and cognitive decline who had sustained a fall complicated by a subdural hematoma. At 1 year post injury, [¹⁸F]-Florbetapir PET imaging was negative for an AD pattern of amyloid accumulation in this subject. Focal [¹⁸F]-Florbetapir retention was noted at the site of impact. In case 1, amyloid imaging provided improved diagnostic accuracy where standard clinical and laboratory criteria were inadequate. In that same case, tau imaging with [18F]-T807 revealed a subcortical tauopathy that we interpret as a novel form of CTE with a distribution of tauopathy that mimics, to some extent, that of progressive supranuclear palsy (PSP), despite a clinical presentation of amnesia without any movement disorder complaints or signs. A key distinguishing feature is that our patient presented with hippocampal involvement, which is more frequently seen in CTE than in PSP. In case 2, focal [18F]-Florbetapir retention at the site of injury in an otherwise negative scan suggests focal amyloid aggregation. In each of these complex cases, a combination of [18F]-fluorodeoxyglucose, [18F]-Florbetapir and/or [18F]-T807 PET molecular imaging improved the accuracy of diagnosis and prevented inappropriate interventions.

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INTRODUCTION

Recent attention has been focused on the cognitive risks involved in contact sports. These concerns have been associated historically with chronic and repetitive concussions in boxers, but recently professional football players, 1,2 hockey players, 3 and wrestlers have become the focus of expanded attention. In addition, the sometimes-fatal consequence of a single, significant traumatic brain injury (TBI) has been highlighted recently by the media due to high profile cases (for example, http://abcnews.go.com/Enter tainment/Movies/story?id = 7119825 and http://www.express.co.uk/comment/columnists/richard-and-judy/451938/F1-racing-dri ver-Michael-Schumacher-ski-crash-highlights-sport-secret-on-headinjuries). On the basis of clinical and postmortem studies, the

conventional wisdom has been that a single severe TBI increases risk for Alzheimer's disease (AD),^{5,6} whereas the consequences of chronic repetitive TBI, first identified in boxers, increases the risk for a tangle-predominant disease, or tauopathy, known as dementia pugilistica.⁷ More recently, the term 'chronic traumatic encephalopathy (CTE)' has been applied when dementia pugilistica-like neuropathology was observed in retired National Football League (NFL) players, as well as in entertainment wrestlers, victims of domestic violence and in military veterans exposed to blast and concussive injuries from improvised explosive devices.^{1,2,4,8–10} Neuropathologically, CTE is characterized by prominent tauopathy, variable degrees of diffuse amyloid deposition, and degeneration of the neocortex, hippocampus,

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amygdala, basal forebrain and mammillary bodies. The nature, distribution and patterns of neurofibrillary degeneration in CTE are distinctive from AD, 11,12 and neuropsychological, mood and neurobehavioral dysfunction in CTE typically presents in midlife after a latency period, usually years or decades after exposure to the repetitive trauma. The cognitive and behavioral symptoms of CTE begin insidiously, followed by progressive deterioration. Mood symptoms typically include depression, apathy, irritability and suicidality. Behavioral symptoms include poor impulse control, disinhibition and aggression, as well as frequent comorbid substance abuse. Nevertheless, CTE remains a controversial diagnosis, as it is a pathological diagnosis, and no consensus on the clinical diagnosis has yet been developed. Therefore, diagnosis may be difficult to determine on the basis of a standard clinical and laboratory evaluation criteria.

The challenge faced by many clinicians in such cases is making an accurate diagnosis from among the various dementias that share cognitive, mood and behavioral symptoms, particularly when considering the differential diagnosis of AD or frontotemporal dementia (FTD) and CTE. To order the appropriate tests and implement the most effective treatment available, clinicians must determine the underlying neuropathology on the basis of clinical evaluation and history, and will ultimately diagnose an individual with a neurodegenerative disease to be proven at the postmortem examination. Three new positron emission tomography (PET) tracers have been approved recently by the US Food and Drug Administration as clinical tools to estimate brain amyloid burden in patients being evaluated for cognitive impairment (CI) or dementia. Imaging with these tracers, if positive, means AD plagues are present; if the scan is negative, cerebral amyloidosis is absent, and a negative scan, such as the one in this case using [18F]-Florbetapir, provides in vivo confirmation that the dementia is not AD, if negative. Such scans increase the accuracy of diagnosis. Amyloid imaging may improve etiological likelihood in situations where the differential diagnosis cannot be resolved on the basis of standard clinical and laboratory criteria. 16 In the absence of brain amyloid it is unlikely that the cause of an individual's cognitive decline is due to AD.¹⁷

Early studies suggested that TBI increased the risk for AD at an earlier age of onset; however, these findings were not based entirely on neuropathological evidence and some were methodologically flawed (for review, see ref. 18). The diagnosis of AD requires the presence of amyloid β neuritic plaques and neurofibrillary tangles in brain. 19 The clinical distinction of AD from other causes of posttraumatic CI can be challenging, but accurate diagnosis is required to avoid misdiagnosis, incorrect prognosis, incorrect family history, and potentially, initiation of inappropriate treatment.

Several new PET imaging neurotracers have been developed that detect pathological tau $in\ vivo$. One such ligand, $[^{18}F]$ –T807, is one of a novel class of 5H-pyrido[4,3-b]indole labeled with $[^{18}F]$ that has a high affinity and selectivity for tau over amyloid $\beta\ (>25$ fold). Preliminary imaging studies in AD transgenic mice and patients found that this ligand has favorable imaging kinetics, high target cortical to cerebellum uptake ratios, and an accumulation pattern that followed the characteristic tau deposition pattern seen in AD. Here we present two clinical cases in which the $in\ vivo$ findings utilizing these new PET tracers for amyloid plaques and neurofibrillary tangles clarified the diagnoses.

CASE REPORT

Case 1

A 71-year-old retired professional football player who had sustained multiple concussions during a decade-long NFL career ending approximately 40 years ago presented with a history of

progressive CI. During his professional career, he reported experiencing multiple concussions but was unable to estimate their number. He did not recall any episodes of loss of consciousness, but did remember being dazed and confused for up to a full day following some of these injuries; having difficulty finding his way home after a game or, upon awakening on the day after some games, being unable to recall the identity of the team against whom he had played the previous day. After retiring from the sport, he had a successful business career (outside of sports) for approximately 20 years. After retiring from business, he coached high school football. Over the past several years, however, he and his wife noticed impaired memory and thinking, notably short-term memory, and more so in the past year. Agitation emerged after his memory decline, and increased in the year before evaluation. There were no other reported behavioral disturbances; mood was normal. He was evaluated for progressive neurodegeneration by the NFL Neurological Care Program team at Mount Sinai Hospital, a multidisciplinary team consisting of a neurologist, a dual-board-certified neurologist-psychiatrist, a neuropsychologist and two neuroradiologists. All evaluators were TBI and AD experts. At the time of the evaluation, the patient was taking both donepezil and memantine, neither of which had any benefit that was obvious to the patient's wife.

The evaluation included comprehensive neurologic and neuropsychological assessment and, given the potential differential diagnosis, a clinical [18F]-Florbetapir PET scan to determine the presence or absence of amyloid. A research [18F]-T807 PET scan was performed to determine the possible presence of tauopathy. Magnetic resonance imaging (MRI) of the brain was conducted 3 months before PET imaging. The MRI revealed global volume loss, especially in the hippocampus. Arachnoid cysts were present in the middle fossa bilaterally. The mammillary bodies were poorly visualized and therefore suspected to be atrophic. The hypothalamic/infundibular/pituitary system appeared preserved structurally. Neurologic exam was grossly normal. Eye movements were normal in all directions. Muscle tone and strength were intact, reflexes were brisk and symmetrical, and no movement disorder was detected upon initial exam. Retrospectively, mild hypomimia was noted.

Case 2

Case 2 was a 59-year-old male physician who had spent nearly 30 years as a member of a group medical practice. He had suffered a head injury while skiing (wearing a helmet) approximately 10 months before the evaluation. Specifically, he fell off a ski lift with head impact on concrete. He later had a fall on the slopes. He denied loss of consciousness (his family noted transient loss of awareness), but reported persistent headache for a few weeks following the head injury. He then began to experience intermittent numbness of his right ear and numbness and weakness in his right hand, for which he sought neurological evaluation approximately 3 months post injury near his residence in another part of the country. MRI revealed recent and chronic bleeding over the left hemispheric convexity, and he underwent a craniotomy to evacuate a left frontal subdural hematoma. The site of the injury was right occipital, thus the subdural hematoma appeared to be a result of a contrecoup injury. Following craniotomy, his headaches persisted as did the intermittent numbness and weakness in his right hand, for which he was begun on levetiracetam.

Detailed history revealed that for many months before the accident his family had noted a change in his personality, episodic increased agitation and altered cognition (word retrieval, short-term memory). They reported that the patient had difficulty recalling recent events but that recall of childhood information remained generally intact. He forgot recent conversations and began having difficulty recognizing the faces of acquaintances,

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patients and old friends, as well as pictures of famous people. He struggled with abstract reasoning (for example, how people and things related to one another) and had trouble following directions. He would ask the same questions repeatedly and told the same stories multiple times without recalling he had done so. He was unable to maintain attention and concentration when a story became increasingly complicated, and would become agitated and irritable as a result of not being able to follow the story line. When confronted about his cognitive difficulties he would become angry and agitated, and would 'act out' in the presence of his family. According to the family, the patient would experience 'manic highs and depressed lows'. When in a good mood, he enjoyed being with others and was largely socially appropriate. His mood could change rapidly, and he would become withdrawn or belligerent. When in a depressed state he expressed suicidal ideation. According to the family, the patient was less emotionally available for things that had been important to him (for example, family relationships). For months before his fall, he had become apathetic and lost interest in hobbies that he previously enjoyed. Approximately 4 years ago (3 years before the fall), the patient had experienced a depressive episode. He had attributed his depression to work-related stress and was treated with sertraline. He had no history of psychiatric hospitalization or psychotherapy. At the time of his evaluation at Mount Sinai Medical Center he was not taking antidepressants.

The patient was referred for a comprehensive neuropsychological assessment (JM) and neurological evaluation (SG, AA) at the Mount Sinai Alzheimer's Disease Research Center, as well as appropriate laboratory studies. CT and MRI revealed atrophy of the anterior poles of both temporal and frontal lobes (Figure 1). Molecular imaging included both [18F]-fluorodeoxyglucose (FDG) PET and [18F]-Florbetapir scans. At the time of the evaluation, his medications were atorvastatin 20 mg daily and acetaminophen PRN. He had had a previous neuropsychological evaluation at another facility, 3 months before our assessment. The findings on the prior examination were consistent with the current evaluation.

RESULTS

Case 1

Neuropsychological function. The patient had 16 years of education and premorbid intellectual function was estimated to be in the average range. Neuropsychological tests revealed impaired information processing speed, fine motor function, verbal comprehension and fluency, confrontational naming, and

immediate and delayed verbal recall. Intellectual function was preserved. On self-report, he acknowledged minimal depression and mild anxiety (Table 1). Norms were corrected for age and years of education.

Following this comprehensive evaluation, the experts disagreed as to whether AD was present, in addition to likely posttraumatic encephalopathy. Two independent neuropsychologists from the Mount Sinai Alzheimer's Disease Research Center (ADRC) reviewed the neuropsychological test results and supported the inclusion of possible AD on the basis of the neuropsychological phenotype, although the primary examining team (with the exception of one of the neurologists) opposed the inclusion of possible AD as a diagnosis. Thus the patient was referred for [18F]-Florbetapir PET imaging for diagnostic clarification.

Molecular imaging. [18F]-Florbetapir imaging was conducted with a GE Discovery STE 16-slice PET/CT camera. The patient was injected with 370 MBq (10 mCi) of $[^{18}F]$ -Florbetapir. Image acquisition began approximately 60 min post injection, for 10 min. Images were acquired in three dimensions, using a oneframe and one-bed position. Reconstruction was performed with a 120 × 120 matrix utilizing iterative reconstruction, with 35 subsets and two iterations. The z axis filter was standard, and a 2.57-mm full width/half maximum filter was used. The field of view was 30 cm in diameter, with 47 total slices.

The clinical [18F]-Florbetapir scan results were rated by nuclear medicine physicians (JM or LK) trained to interpret [18F]-Florbetapir scan results using a binary (positive or negative) visual approach.²⁰ Transaxial, coronal and sagittal images were examined. The scan results were considered positive if uptake in the cerebral gray matter equaled or exceeded the uptake in the white matter in at least two major areas of the brain. A positive [18F]-Florbetapir scan indicates moderate-to-frequent fibrillar amyloid plaques; a negative [18F]-Florbetapir scan indicates sparse-to-no fibrillar amyloid plagues, which is inconsistent with a diagnosis of AD. A negative scan thus implied that the cognitive decline was not due to AD. In the retired NFL player under consideration here [18F]-Florbetapir PET scanning was negative for cerebral amyloidosis (Figure 2), thereby excluding AD. This case illustrates the potential for brain amyloid imaging to clarify diagnosis and to prevent inappropriate treatment. Ironically, this patient had sought out this evaluation to assess his eligibility for a clinical trial for AD. The [18F]-Florbetapir results ruled out his inclusion in trials of Aβ-reducing agents.

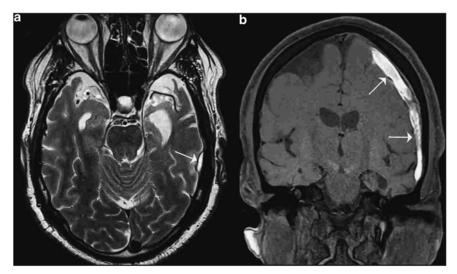


Figure 1. Imaging from a 59-year-old, physician with a sports-related injury (case 2). Magnetic resonance imaging showing atrophy of the frontal poles of the frontal and temporal lobes bilaterally. (a) and (b) Arrows indicate a subdural hematoma (SDH).



 Table 1.
 Neuropsychological scores and percentiles for case 1

 (multiple concussions)

(multiple concussions)			
Case 1–age 71 years			
	Score	Percentile	
WAIS-IV indices			
Full scale	103	58	
Verbal comprehension	83	13	
Perceptual reasoning	105	63	
Working memory	128	97	
Processing speed	102	55	
General ability	94	34	
WMIS-IV indices			
Auditory memory	69	2	
Visual memory	58	< 1	
Visual working memory	85	16	
Immediate memory	69	2	
Delayed memory	58	< 1	
Other neuropsychological tests ^a			
Memory			
CVLT-LDFR	0	< 1	
Rey-O delay		< 1	
Language			
FAS		19	
Anima l s		6	
BNT		< 1	
Motor function			
Perdue dom/non-dom		3rd/8th	
General dom/non-dom		21st/2nd	
Visual perception			
REY-O copy		WNL	
Attention			
CPT		WNL	
Executive function			
SCT		96	
DK-FST		91	
Tower task		63	
Trails B		70	

Abbreviations: BNT, Boston Naming Test; CPT, Connors' Continuous Performance Test II; CVLT-LDFR, California Verbal Learning Test long delay free recall; DK-FST, Delis Kaplan Free Sort Test (norms corrected for age and years of education); FAS, Controlled Oral Word Association Test; GPB, grooved pegboard; SCT, Short Category Test; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edn; WNL, within normal limits. ^aScores under other neuropsychological tests reported only as percentiles. Raw scores were not available.

[18F]-T807 imaging was acquired with a Siemens ECAT EXACT HR+ PET Camera. The patient was injected with 370 MBg (10 mCi) of [18F]-T807. Image acquisition began ~110 min post injection, for 20 min. Images were acquired in three dimensions, using oneframe and one-bed position. Reconstruction was performed with a 128 × 128 matrix utilizing iterative reconstruction, with 16 subsets and 4 iterations. A three-dimensional post hoc Gaussian filter (5 mm) was applied to the image volume. A total of 63 axial slices of 2.42 mm thickness were displayed for visual interrogation by a nuclear medicine physician expert in brain imaging (JS). In addition, quantification of the scan was performed by spatially normalizing the PET image to a T807 template image and applying a modified Hammers volume of interest template²¹ for extraction on regional standard uptake values (SUV). Brain SUV were divided by the cerebellar cortex SUV to calculate SUV ratios in multiple cortical and subcortical regions.

Visually, the [¹⁸F]-T807 PET scan revealed [¹⁸F] signal in some temporal areas. However, the preponderance of the signal arose bilaterally from the regions of the globus pallidus and the

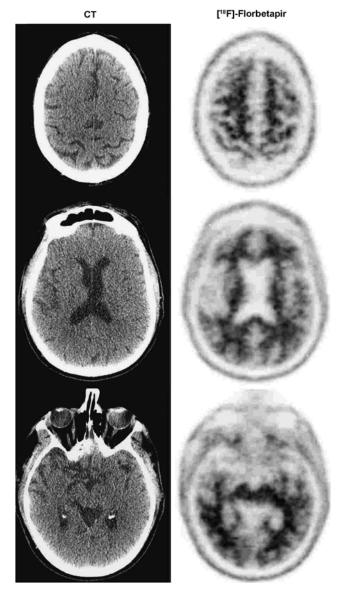


Figure 2. Imaging from a 71-year-old retired NFL player (case 1). Left panel is CT image and right panel is [¹⁸F]-Florbetapir PET imaging, which was negative for amyloid accumulation. CT, computed tomography; NFL, National Football League; PET, positron emission tomography.

substantia nigra (Figure 3). Consistent with this visual assessment, the region with highest SUV ratios were globus pallidus (1.85), putamen (1.57) and hippocampus (1.45), while the substantia nigra SUV ratio was 1.40.

Case 2

Neuropsychological function. His premorbid intellectual function was estimated to be in the high average range. He manifested significant deficits in memory, language (verbal fluency and confrontation naming), and executive functioning; performance on most cognitive measures was far below levels expected for his age, education and estimated premorbid abilities; they ranged from significantly impaired to high average (Table 2). Results were consistent with previous testing, which was suggestive of FTD. On self-report, he endorsed minimal depression that fell within the



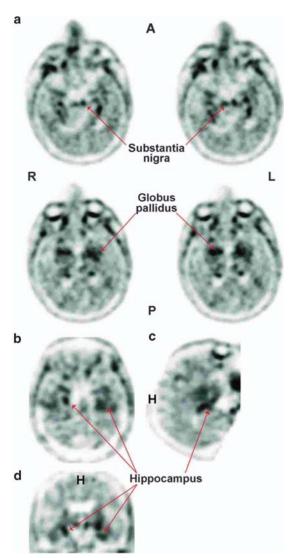


Figure 3. Imaging from a 71-year-old retired NFL player (case 1). F]-T807 signals (arrows) originate from the globus pallidus (GP), substantia nigra (SN) and hippocampus. Images depict axial (a) sagittal (b) and coronal (c and d) orientation of the brain. A, anterior; H, head; L, left; NFL, National Football League; P, posterior; R, right.

normal range (Table 2). Norms were corrected for age and years of education.

Molecular imaging

[18F]-FDG PET imaging: [18F]-FDG PET and [18F]-Florbetapir PET imaging were performed on consecutive days. All imaging procedure details were identical to those described for case 1. The patient was injected with 440.3 MBg (11.9 mCi) of [18F]-FDG. Forty minutes later, PET images of the brain were obtained.

FDG PET showed decreased uptake in the medial portions of both frontal lobes, mildly on the right, moderately on the left (left > right), decreased uptake in the posterior portion of the left temporal lobe and mildly decreased activity in the right anterior temporal lobe. Otherwise, the distribution of radiotracer was normal in cortical and subcortical structures (Figure 4). The impression was of abnormal FDG PET scan that demonstrated decreased metabolism in the medial portions of the frontal lobes, more pronounced in the left side than the right, and the posterior portion of the left temporal lobe. The patchy nature of hypometabolic regions raised the possibility of a vascular etiology.

Table 2. Neuropsychological scores and percentiles for case 2 (single TBI)

Case 2—age 59	years	
	Score	Percentile
WAIS-IV indices		
Full scale	NC	NC
Verbal comprehension	63	1
Perceptual reasoning	105	63
Processing speed	92	30
Estimated premorbid IQ and orientation		
AMNART estimated premorbid IQ	107	68
MMSE	23/30	0/3 reca l l
WMIS-IV subsets	Scaled score	
Logical memory I	6	9
Logical memory II	6	9
Recognition	Ü	51–75
Other neuropsychological tests ^a	Z-score/T-score	
Memory CVLT -II trial 1–5	T=34	5
CVLT short delay free recall	-2	2
CVLT long delay free recall	– 1.5	6
Language	Raw score	
FAS Anima l s	31 10	11 < 2
BNT	3 out of 60	< 1
Rey-O delay	9	3
Visual perception		
REY-O copy	34	WNL
WAIS-IV block design Attention	33	37
WAIS-IV digit span	28	63
WAIS-IV arithmetic	9	9
CVLT-proactive interference	- 25	50
CVLT-retroactive interference	-71.4	30
Executive function		
WCST Trails B	74′	56
Mood	/4	20
BDI-II	3	WNL

Abbreviations: AMNART, American National Adult Reading Test; BDI-II, Beck Depression Inventory (norms corrected for age and years of education); BNT, Boston Naming Test; CVLT, California Verbal Learning Test; FAS, Controlled Oral Word Association Test (letters FAS); MMSE, Mini Mental Status Examination; TBI, traumatic brain injury; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edn; WCST, Wisconsin Sorting Test; WMS-IV, Wechsler Memory Scale, 4th edn; WNL, within normal limits. ^aFull scale IQ NC is not calculated due to a 42-point discrepancy between verbal and nonverbal abilities; nonverbal abilities stronger.

[18F]-Florbetapir PET imaging: The patient received 403.3 MBq (10.9 mCi) of [18F]-Florbetapir through intravenous injection. Sixty minutes later, PET images of the brain were obtained. The [18F]-Florbetapir PET images showed normal distribution of radiotracer uptake throughout the cortical and subcortical structures, except for a small area of increased cortical uptake in the right occipital region. The scan was read as negative for significant amyloid



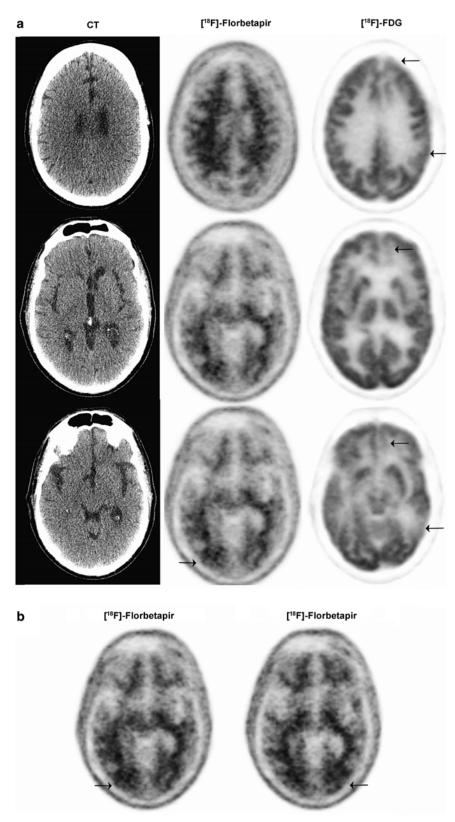


Figure 4. Imaging from a 59-year-old, physician with a sports-related injury (case 2). [¹⁸F]-Florbetapir PET imaging findings were negative for amyloid accumulation except for focal [¹⁸F]-Florbetapir retention at the site of impact in the occipital region (arrows). (**a**) CT (left panel) [¹⁸F]-Florbetapir PET (middle panel) and FDG PET (right panel) at various depths of the brain. (**b**) [¹⁸F]-Florbetapir PET indicating amyloid accumulation. CT, computed tomography; FDG, [¹⁸F]-fluorodeoxyglucose; PET, positron emission tomography.

deposition, thus the diagnosis of AD was not supported. However, there was amyloid accumulation focally and specifically in the region of the patient's TBI (right occipital) but also on the left side as well (Figure 4). The final diagnosis was frontotemporal lobar degeneration. What appeared to be a rapidly progressive dementing process looking like AD after a head injury (before [¹⁸F]-Florbetapir PET imaging) was ultimately diagnosed as frontotemporal lobar degeneration, albeit with focal posttraumatic amyloidosis. Although focal amyloidosis is the most parsimonious interpretation, we cannot exclude the possibility that the [18F]-Florbetapir is binding instead to chronic astrocytosis or hemosiderin in the resolving contusion in that region.

DISCUSSION

We present two cases in which amyloid imaging clarified uncertain diagnoses. Case 1 may be the first assessment demonstrating, during life, lack of AD pathology in an NFL player with a remote history of multiple concussions and current cognitive decline that had many of the features of AD. A panel of expert clinicians were unable to reach unanimity on the inclusion of possible AD as a diagnosis. The patient's clinical presentation with memory loss was suggestive of AD. The absence of amyloid as revealed by [18F]-Florbetapir PET imaging excluded AD pathology and thereby prevented his inappropriate inclusion in an amyloid-lowering medication clinical trial.

Omalu et al.1 revived the term CTE (originated by Critchley in 1949, in a book chapter entitled, 'Punch-drunk syndrome: The chronic traumatic encephalopathy of boxers') in their report of the case of a retired NFL player with progressive neurological dysfunction. Thereafter, evidence of CTE in American football players became increasingly evident. 1,2,4,22,23 Currently, the challenge is no longer the acceptance of CTE as a diagnostic entity associated with repetitive head trauma, but rather a much needed accounting of the actual numbers of affected persons as well as the numbers of those who remain unaffected despite exposure to identical repetitive head traumas.²⁴

With regard to the short-term memory problems in case 1, Guskiewicz et al.²⁵ reported a strong relationship between TBI history and memory complaints in former NFL players. In that study, individuals with a history of at least three concussions were three times more likely to report significant memory problems and five times more likely than those with no history of concussions to have been diagnosed with mild Cl.²⁵ In their review of 48 cases of neuropathologically confirmed CTE, McKee et al.9 found that memory loss was reported in over half of the individuals. As in AD, loss of insight often precluded patients from recognizing their deficits; this valuable information was derived from friends or family, and the patients frequently demonstrated anosognosia during the course of the evaluation.

Impairment in executive function was common in cases of neuropathologically confirmed CTE.⁸ Executive functions are a collective set of higher-order abilities (judgment, self-inhibitory behaviors, decision-making, planning and organization) considered to be dependent primarily upon adequate functioning of frontal lobe networks. Damage to various regions of the frontal cortex can disrupt these higher-order abilities, leading to poor impulse control, and socially inappropriate, avolitional and/or apathetic behaviors. For example, damage to the orbitofrontal regions can result in significant changes in personality. Thus, changes in personality, apathy, impulsivity, aggression and 'short fuse' behaviors typical of CTE¹⁴ are consistent with the atrophy, structural damage and other neuropathological changes of the frontal lobes that have been described in nearly all reported cases of CTE.^{8,9,14} Given these findings, the overlap in neurocognitive and behavioral symptoms may make the distinction among AD, CTE and FTD difficult, in the absence of molecular evidence of disease-specific proteins. In the cases reported here Florbetapir

imaging served as an in vivo method of discrimination that resulted in diagnostic clarification that would ultimately guide treatment planning and intervention.

The [18F]-T807 imaging in case 1 yielded somewhat unexpected results. The preponderance of the ligand retention was subcortical and localized to the basal ganglia and substantia nigra. This distribution is not typical for CTE and is more similar to that of progressive supranuclear palsy, although our case did not manifest the typical clinical symptoms of progressive supranuclear palsy. Ling et al.26 recently reported a patient with concurrent CTE and progressive supranuclear palsy, in whom they proposed that this atypical phenotype arose because of the superimposition of the brain trauma and CTE on a genetic background already predisposed toward progressive supranuclear palsy. The prominent amnesia, the absence of a movement disorder and the involvement of the hippocampi in the [18F]-T807 retention all support the formulation of the diagnosis of CTE. Such a coincidence has also been proposed for the handful of concurrent cases of CTE and amyotrophic lateral sclerosis.¹¹ This result emphasizes the need for novel ligands such as [18F]-T807 and for heightened suspicion for atypical phenotypes in the clinical setting of TBI. Other ligands that recognize microglia or TDP43 (ref. 11) might also be useful in providing a fuller appreciation of the spectrum of CTE. Indeed, the neuroimaging of CTE may lead to expansion and/or revision of the definition and staging 10 of CTE beyond the current pathology-based system.

In case 2, the patient had a history of personality change and a fall from a ski lift with head impact on concrete and some alteration in level of consciousness. When referred, the tentative diagnosis was AD. This initial formulation was ultimately rejected once it was clarified that the personality change preceded the TBI and the patient was given a diagnosis of FTD. The Florbetapir scan revealed only a small focal occipital retention of ligand at the site of impact. There was no amyloidosis elsewhere in the brain, and the MRI and FDG PET showed atrophy and hypometabolism in the frontal and temporal poles, consistent with a frontotemporal lobar degeneration etiology for his clinical FTD syndrome. The best explanation was that this patient had FTD due to frontotemporal lobar degeneration compounded by the diffuse and focal injuries induced and perhaps accelerated by the TBI; the focal occipital cortical amyloidosis itself had an uncertain contribution to his clinical symptoms.

Our findings in case 2 are somewhat consistent with those of Hong et al.27 who performed PET imaging in patients who had sustained moderate-to-severe TBI within 1 year of injury; they utilized [11C] Pittsburgh compound B (abbreviated PiB; the [18F] version of PiB is known as Flutemetamol or Vizamyl) PET imaging, the first amyloid labeling ligand to be developed. They found increased distribution of [11C]-PiB following TBI, the specificity of which was validated by neocortical binding of tritium-labeled PiB in regions of amyloid deposition in the postmortem tissue of another cohort of patients who had sustained a TBI and died at intervals of 3 h to 56 days after injury.²⁸ Our patient had sustained TBI within 1 year of our evaluation and [18F]-Florbetapir PET imaging.

Our CTE/molecular imaging experience has included [18F]-Florbetapir PET imaging of young, active boxers post knockout (n=3, ages 35, 36 and 42 years), but these studies have been unrevealing (Jordan and Gandy, unpublished observations). A number of uncontrolled variables, including levels of amyloid upregulation insufficient to aggregate into diffuse plaque, rapid clearance of any aggregated amyloid post TBI, or insufficient sensitivity of florbetapir to detect low levels of diffuse amyloid could explain this.

In conclusion, amyloid imaging offers in vivo affirmative confirmation of the presence or absence of amyloid deposition and may increase the accuracy of the likely cause of CI or dementia in patients with a history of TBI. Future evaluation in



repetitive head trauma where CTE is suspected may be best served by tau imaging because beta-amyloid is usually relatively sparse or absent in CTE brains. Therefore, selective tau binding ligands may be more useful for diagnosis or ruling out CTE. We are now testing this hypothesis in a new cohort of patients and research subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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EXHIBIT 9

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Traumatic Brain Injury (IR Couch, Section Editor)

Current Understanding of Chronic Traumatic Encephalopathy

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Keywords Chronic traumatic encephalopathy (CTE) - Concussion - Brain trauma - Traumatic brain injury (TBI) - APOE - Biomarker - Tau - Football

Opinion statement

Chronic traumatic encephalopathy (CTE) is a unique neurodegenerative disease found in individuals with a history of repetitive head impacts. The neuropathology of CTE is increasingly well defined. Prospective, longitudinal studies with post-mortem neuropathologic validation as well as in vivo diagnostic techniques are needed in order to advance the understanding of CTE clinically. Given the large number of individuals who incur concussions and other forms of brain trauma, this is an important area for scientific and public health inquiry.

Linkfolditerion

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease thought to be associated with a history of repetitive head impacts [1-8, 9**, 10, 11, 12*], such as those sustained through contact sports

or military combat. CTE, a distinct neurodegeneration, was first introduced in the literature as "punch drunk" or dementia pugilistica in the early 1900s because of its association with boxing [13]. In fact, much of the

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early literature about the disease focused on the boxing population [1, 13, 14]. However, the disease is found in a more diverse group of individuals with a history of repetitive head impacts including a variety of contact sport athletes, military veterans, domestic abuse victims, and individuals with self-inflicted head banging behavior [7]. Although significant media attention has been brought to this disease, there is relatively little known regarding the pathobiological mechanisms underlying CTE, and a large number of questions remain. The preponderance of the literature

has consisted of postmortem neuropathologic assessments with retrospective clinical interviews. As such, the neuropathology of CTE is currently better understood than the clinical presentation or course, and there is a need for prospective longitudinal clinical studies with in vivo diagnostic techniques or neuropathologic validation. This article reviews the current state of our knowledge concerning CTE, including neuropathologic characteristics, clinical features, proposed clinical and pathologic diagnostic criteria, possible risk factors, and future research needs.

Neuropathologic characteristics

Much of the scientific literature on CTE, to-date, is derived from clincopathologic case series of the disease [1–4, 6–8, 9••, 15]. The neuropathology of CTE is increasingly well defined. In 2013, McKee and colleagues published the largest case report to date of individuals with neuropathologically confirmed CTE, presenting proposed criteria for four stages of CTE pathology based on the severity of the findings [9••]. Formal validation of the reliability of these criteria and the staging system are currently being performed by a team of nine neuropathologists, funded by a National Institutes of Health (NIH) U01 grant (1U01NS086659-01, National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Biomedical Imaging and Bioengineering (NIBIB); PI, Ann McKee). Detailed criteria of McKee et al.'s pathologic staging criteria can be found in Table 1.

CTE is characterized by the deposition of hyperphosphorylated tau (ptau) protein as neurofibrillary tangles (NFT) beginning perivascularly and at the depths of the cortical sulci. Later stage p-tau pathology becomes more widespread, particularly dense in the medial temporal lobes, also present in the white matter, and leads to prominent neuronal loss and gliosis. The irregular and perivascular nature of the p-tau neurofibrillary tangles, the proclivity for the sulcal depths, and the marked subpial and periventricular involvement are unique features of the disease that distinguish it from other tauopathies. TAR DNA-binding protein 43 (TDP-43) is present in about 80 % of cases. Early stages show sparse TDP-43 positive neurites in cortex, medial temporal lobe, and brainstem. Late-stage pathology presents with TDP-43 intraneuronal and intraglial inclusions in the frontal subcortical white matter and fornix, brainstem, and medial temporal lobe. In most cases of CTE, there are no beta amyloid 1-42 (A β_{1-42}) positive neuritic plaques. Evidence of axonal injury is common and ranges from multifocal axonal varicosities in earlier stage pathology to severe axonal loss in later stage pathology. Stage I and II CTE can present macroscopically with mild enlargement of the lateral ventricles or third ventricle and/or mild septal abnormalities. Grossly, advanced CTE is characterized by enlargement of the lateral and third ventricles, cavum septum pellucidum, septal perforations, and pallor of the substantia nigra and locus coeruleus. In addition, severe

	Stage II	Stage III	Stage IV
Focal perivascular NFTs at depths of cortical sulci	NFTs adjacent to focal epicenters and in nucleus basalis of Meynert and locus coeruleus	Dense in medial temporal lobes and widespread in cortex, diencephalon, brainstem, and spinal cord	P-Tau pathology widespread including in white matter; prominent neuronal loss and gliosis of cortex; hippocampal sclerosis
Mild lateral ventricle enlargement in some cases	Mild enlargement of the frontal horn of the lateral ventricles or third ventricle in a majority of cases; small cavum septum pellucidum in some cases	Mild cerebral atrophy; enlarged ventricles; depigmentation of locus coeruleus and substantia nigra; septal abnormalities in some cases	Increased cerebral, medial temporal lobe, hypothalamus, thalamus, and mammillary body atrophy; septal abnormalities; enlarged ventricles; pallor of locus coeruleus and substantia nigra
Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Severe intraneuronal and intraglial inclusions in cortex, white matter, diencephalon, basal ganglia, brainstem
Multifocal axonal varicosities in cortex and subcortical white matter	Multifocal axonal varicosities in cortex and subcortical white matter	Severe axonal loss in cortex and white matter	Severe axonal loss in cortex and white matter
	NFTs at depths of cortical sulci Mild lateral ventricle enlargement in some cases Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem Multifocal axonal varicosities in cortex and subcortical	NFTs at depths of cortical sulci nucleus basalis of Meynert and locus coeruleus Mild lateral ventricle enlargement in some cases the lateral ventricles or third ventricle in a majority of cases; small cavum septum pellucidum in some cases Sparse TDP-43 Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem Multifocal axonal varicosities in cortex and subcortical Multifocal axonal varicosities in cortex and subcortical white	NFTs at depths of cortical sulci nucleus basalis of Meynert and locus coeruleus brainstem, and spinal cord Mild lateral ventricle enlargement in some cases the lateral ventricles in a majority of cases; small cavum septum septum septum pellucidum in some cases Sparse TDP-43 Sparse TDP-43 neurites in cortex, medial temporal temporal lobe, brainstem brainstem Sparse TDP-43 Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem Multifocal axonal varicosities in cortex and subcortical white matter

cases may also show profound atrophy of the medial temporal lobes or profound global atrophy. In reports examining former football players [9**] and former boxers [1], the severity of pathology appears to correlate to duration of athletic career. McKee et al. also found an association between severity of pathology to years since retirement from athletics and age at death [9**].

Clinical presentation

Clinical symptoms of CTE generally present years or decades after exposure to trauma [1, 9.0, 16.0]. Although there are some symptom overlaps between the acute concussive injury and the later-life neurodegenerative process of CTE (eg., attention and concentration loss, headache), it is thought that CTE is distinct from the acute concussion or postconcussion sequelae [17]. That is,

although a history of repetitive brain trauma is thought to be necessary to cause CTE (ie, all neuropathologically confirmed cases of CTE to date have had a history of repetitive brain trauma), CTE symptoms are not just the cumulative effects of this process. Furthermore, there is no clear relationship between prolonged acute concussion symptoms (eg, postconcussion syndrome) and the pathology of CTE.

Evidence to-date suggests that CTE presents clinically with symptoms in one or more of four possible domains: mood, behavior, cognition, and motor [9.0, 16.0]. Commonly noted mood features include depression, irritability, and hopelessness. Behavioral features may include impulsivity, explosivity, and aggression. Cognitive features can include memory impairment, executive dysfunction, and in severe cases dementia. Motor features, including parkinsonism, ataxia, and dysarthria, appear in a subset of cases, predominantly boxers. In addition, chronic headache is also experienced in some cases [7, 9.0, 15, 18, 16.0, 19, 20.0, 21.0]. Two distinct clinical presentations of CTE have been described in a recent study by Stern et al., substantiating evidence from earlier literature regarding this possibility [1, 16.0, 22-24] According to Stern and colleagues, the first type of clinical presentation initially presents with mood and behavioral symptoms earlier in life (mean age approximately 35) and progresses to include cognitive symptoms later in the disease course. The second clinical presentation begins with cognitive impairment later in life (mean age approximately 60), which may progress to include mood and behavioral symptoms [16••].

Earlier cases of CTE tended to report a higher prevalence of motor features than more recent reports. Differences in symptom profile have led some researchers to differentiate "classic" and "modern" CTE clinically [25•]. It is worth noting that "classic" cases were predominantly boxers, whereas more recent descriptions have been dominated by football players. Differences in the nature of exposure could account for differences in presentation—biomechanical comparisons of head impact dynamics in boxing and football have shown that boxers experience proportionally more rotational acceleration than in football [26, 27]. Further, computational modeling of boxing impacts suggests that stress in boxing impacts is greatest on midbrain structures, and midbrain damage may account for the parkinsonian features found in CTE [27, 28]. Supporting this theory, in the case series of neuropathologically confirmed CTE by McKee and colleagues [9...], professional boxers and professional football players with neuropathologically confirmed CTE, professional boxers exhibited significantly more motor symptoms (eg. ataxia dysarthria) relative to football players. This clinical difference between boxers and football players was mirrored in the pathology: boxers displayed more cerebellar scarring than football players. Thus, although there is a notable difference in the presence of motor symptoms between the earlier and more recent CTE literature, this may be attributable, at least in part, to the variance in head impact exposure types experienced by boxers and football players.

The question of suicide in CTE remains contentious [29•]. Several CTE case series have included victims of suicide.[6, 7, 9••, 16••] However, our lack of understanding of the population incidence of CTE limits our ability to attribute a complex and multifactorial behavior such as suicide to underlying CTE proteinopathy. The issue is further complicated considering that well

established risk factors for suicide and suicidal ideation such as substance use and depression [30, 31] are often comorbid in cases of CTE [9**, 16**]. The current literature does not provide means to separate the contribution (or lack thereof) of these different potential factors to the act of completing suicide. Further, premature association between repetitive brain trauma and suicidality could result in a 'self-fulfilling prophecy' prompting wider suicides in exposed individuals irrespective of contribution (or noncontribution) from CTE symptoms. Available scientific evidence cannot wholly support the notion that CTE causes suicidal thoughts or behaviors, and such assumptions or assertions should be avoided without further evidence.

All efforts to define the clinical presentation of CTE are also limited due to the lack of in vivo diagnosis and use of retrospective reviews of case reports[15, 20•, 21•] or family interviews [9••, 16••]. This information is valuable to determine initial correlations between presence of neuropathology and clinical manifestation; however, because of their retrospective third-party nature, there are significant limitations to these data. Although some of the earlier literature includes clinical evaluations [13, 32], the findings and their generalizability is limited by the technology of the era [25•]. Increased prospective and longitudinal clinical research in this area is critically needed.

Clinical diagnosis and in vivo biomarkers

Several important studies are underway to develop reliable biomarkers for CTE during life, although like most neurodegenerative diseases, the definitive diagnosis of CTE is based on neuropathologic examination. To date, three groups of authors have proposed preliminary clinical and/or research diagnostic criteria [20•, 21•, 33•]. The three independently proposed criteria are largely comparable and follow a structure similar to the National Institutes on Aging-Alzheimer's Association clinical diagnostic criteria [34] by differentiating between probable and possible cases based on endorsement of various signs and symptoms. All criteria require a patient to have a history of brain trauma, and to exhibit symptoms consistent with the clinical presentation of CTE described in the literature that could not likely be explained by another condition. All three criteria identified behavioral and cognitive disturbances as important for a diagnosis of CTE. Research groups differ concerning the importance of motor features; Jordan has suggested that motor features resulting from injury to the pyramidal tracts, extrapyramidal system, and cerebellum are necessary for CTE, whereas both Montenigro et al. and Victoroff have suggested a less central role of motor features in diagnosing clinical CTE [20•, 21•, 33•]. Montinegro et al. suggested codifying the clinical syndrome associated with repetitive brain trauma as Traumatic Encephalopathy Syndrome (TES), and reserving CTE for postmortem neuropathologic diagnoses [33•]. In order to confirm the utility of these criteria in either research or clinical settings, future studies will need to demonstrate an ability to reliably differentiate between cases and noncases with a high degree of specificity. A comparison of these proposed criteria can be found in Table 2.

Disease/disorder	Jordan (2013) CTE	Montenigro et al. (2014) Traumatic encephalopathy syndrome (TES), a clinical syndrome associated with history of repetitive brain	Victoroff (2013) CTE
Subclassifications	Definite, Probable, Possible, Improbable	trauma behavioral/mood variant (BMv), cognitive variant (COGv), mixed variant (MIXv), dementia (D); differentiated depending on the presence of motor features or clinical course, or probable, possible, or unlikely CTE based on biomarkers.	Clinically probable, Clinically possible; acute onset, delayed onset; apparently persistent, apparently progressive, apparently improving.
History of brain trauma	No specific guidance as to the specific type or amount of brain trauma required.	History of multiple head impacts (mTBI, TBI, or subconcussive trauma) from high exposure contact sports, other significant exposure to repetitive hits, or any activity resulting in TBI.	Probable or definite exposure to one or more of the following: TBI, concussion, subconcussion.
Duration of symptoms	No guidance provided.	Symptoms must be present for	Symptoms must last for at least
onset of symptoms	Typically manifest later in life after a period of latency.	a minimum of 12 months. Symptom onset must be delayed by at least 2 years from exposure to brain trauma.	two years after impact. Acute onset cases have no period of recovery in the 6-12 months following concussion. Delayed onset cases have evidence of decline following apparent recovery postimpact.
Differential diagnosis	Definite (neuropathologically confirmed) and Probable cases of CTE involve ruling out of other possible neurological causes. Possible CTE can potentially be explained by other known neurological causes. Improbable CTE can be explained by a pathophysiological process unrelated to brain trauma.	Must rule out other neurological disorders, including residual symptoms from acute TBI or postconcussion syndrome that could account for symptoms. Comorbidities such as substance use, other neurodegenerative diseases can be present.	Must rule out other medical or psychiatric diagnosis that could explain symptoms.
Clinical features	unrelated to brain trauma. Behavioral and psychiatric features: aggression or agitation, apathy, impulsivity, depression, delusions, suicidality.	Core clinical features: Difficulties in cognition substantiated with scores of ≥1.5 SD below norms on standardized mental status	Symptoms: headache, speech changes, tremor, deterioration in stance or gait, falls, cognitive decline, mood changes, anxiety

Table 2. (Continued)

Jordan (2013)

Cognitive features: impaired attention and concentration, memory problems, executive dysfunction, dementia, visuospatial difficulties, language impairment. Motor features: dysarthria, spasticity, ataxia, parkinsonism, gait disturbance, motor neuron disease (possibly).

Symptom requirements for diagnosis Definite: neurological process consistent with clinical presentation of CTE along with pathological confirmation. Probable: two or more of the following conditions: cognitive and/or behavioral impairment, cerebellar dysfunction, pyramidal tract disease or extrapyramidal disease; distinguishable from other disease processes and consistent with the clinical presentation of CTE. Possible: neurological process consistent with clinical presentation of CTE but potentially explained by other neurological disorders. Improbable: inconsistent with clinical description of CTE and be explained by a process unrelated to brain trauma.

Montenigro et al. (2014)

or neuropsychological tests; behavior issues (eg, short fuse, violence); mood disturbance (eg, depression). Supportive features: impulsivity, anxiety, apathy, paranoia, suicidality, chronic headache, motor signs (eg, parkonsinism), documented functional decline, delayed onset. Potential Biomarkers for Diagnosis of Probable CTE: cavum septum pellucidum, normal beta amyloid CSF levels, elevated CSF p-tau/tau ratio, negative amyloid imaging, positive tau imaging, cortical atrophy based on neuroimaging, cortical thinning based on neuroimaging.

At least one core clinical feature must be present and considered a change from baseline functioning, at least two supportive features must be present. TES-BMv: behavioral and/or mood core features without cognitive core features. TES-COGV: cognitive core features without behavioral and/or mood core features. TES-MIXv: both cognitive core features and behavioral and/or mood core features. TES-D: progressive course of cognitive core features, evidence of functional impairment. Probable CTE: meets TES criteria, progressive, >1 positive CTE biomarker. Possible CTE: meets TES criteria, either has not undergone biomarker testing or has had a negative biomarker (other than tau imaging) or has another disorder that may account for presentation. Unlikely CTE: does not meet TES criteria and/or

has had negative tau imaging.

Victoroff (2013)

paranoia, personality change (eg, imitability, apathy), alcohol abuse dependence or sensitivity, anger or aggression. Neurological signs: nystagmus, dysarthria, reduced facial expression, hypertonia or rigidity, hyperreflexia, hemiparesis, tremor, limb ataxia, disorders of gait or stance. Neurobehavioral signs: memory loss, other cognitive impairment (eq disorientation, confusion), mood disturbance (eq depression), thought disorder, pathological personality traits (eq. irritability, apathy), anger or aggression.

Clinically probable diagnosis requires at least two symptoms and three signs. Clinically possible diagnosis requires at least one symptom and two signs. Cases should be identified as acute onset or delayed onset. (See onset of symptoms above.) Cases should be identified as either apparently persistent (clinical features last more than two years), apparently progressive (clinical features last for more than two years and are unequivocally progressing), or apparently improving.

CTE chronic traumatic encephalopathy.

To date, there are no objective, validated in vivo biomarkers of CTE. However, important work in the area of CTE biomarkers is currently underway. Several research groups [18, 21*, 35*, 36] have suggested that negative amyloid PET imaging in the presence of positive tau PET imaging could provide a reliable way to differentiate between cases of CTE and Alzheimer's disease (AD). Small and colleagues published preliminary findings in a study of five former professional football players using the PET ligand ¹⁸F-FDDNP, which binds to both tau and amyloid [35°, 37]. Although they suggested that positive findings (higher signals) using this technology could be indicative of underlying CTE pathology, the nonspecific binding of ¹⁸F-FDDNP means that the signal cannot be solely attributed to the presence of tau. Thus, neuropathologic confirmation is needed to determine the underlying pathology. Alternatively, a tau-specific PET ligand, such as those in preliminary studies by Chien et al. [38 ••], may be used to measure tau in vivo as a potential biomarker for CTE. Preliminary work using diffusion tensor imaging has shown evidence of persistent changes in white matter integrity after periods of head impact exposure [39*, 40*], which may prove useful in distinguishing CTE. Magnetic resonance spectroscopy (MRS), a method of measuring brain metabolites, has shown promise in preliminary studies by Lin and colleagues [41•]. Cerebrospinal fluid (CSF) markers have been useful in the AD diagnostic process [34] and CSF p-tau levels have been shown to correlate with levels of p-tau NFT deposition in the brain [42]. Thus, CSF protein measures may useful biomarkers for CIE, and in the differentiation of CIE from other neurodegenerative diseases.

Risk factors

As stated above, to-date, all individuals with neuropathologically confirmed CTE have a history of repetitive head impacts. Although this type of exposure seems to be *necessary* for the occurrence of CTE, it does not appear to be *sufficient*. That is, not all individuals with a history of repetitive head impact exposure get CTE. As previously noted, detailed relation between head impact exposure (eg, frequency, magnitude, age of first exposure) and later-life neurologic outcomes is not well understood. To date, other risk factors for CTE, beyond head impact exposure, are unknown.

Genetics

Genetic risk factors may play a role in development of CTE. The apolipoprotein (ApoE) ϵ 4 allele is the most powerful predictor of sporadic AD [43]. There have been several reports linking the ApoE ϵ 4 allele and head injury with a variety of negative outcomes, including prolonged recovery and poor cognitive performance [44–47]; however, these studies lacked neuropathologic disease confirmation of disease. Findings in neuropathologically confirmed studies are mixed. In the series studied by Stern et al. [16••] and McKee et al. [7], there was an overrepresentation of ϵ 4 carriers in a cohort of neuropathologically confirmed CTE relative to population norms. However, in a study with a larger sample size (N=103), the effect failed to reach significance [9••]. While early clinical findings established a link between clinical outcomes and APOE ϵ 4

expression, the literature has not definitively established a link between APOE genotype and CTE pathology. Future research should examine the association between APOE genotype and CTE, as well as other possible genetic risk factors for CTE such as the MAPT gene or the TARDBP gene.

Livestyle

One important challenge to accurately describing the clinical presentation and course of CTE are the lifestyle comorbidities associated with contact sport athletes and military veterans, in whom the disease has been most studied. Comorbidities such as alcohol abuse or dependence, recreational drug use, and performance enhancing drug use can all lead to personality changes and neuropsychiatric difficulties [48–51]. A non-negligible portion of individuals with neuropathologically confirmed CTE have had reported substance abuse [16••]. However, there are neuropathologically confirmed cases of CTE without a history of any of these afflictions, indicating that they are not causative factors. Therefore, understanding whether and to what extent lifestyle issues, such as those noted, influence the clinical manifestations of CTE is necessary.

Conclusions

Both in CTE and other neurodegenerative diseases, neuropathologic abnormalities are not always directly correlated with specific clinical signs and symptoms. There are likely other factors that influence disease occurrence, progression, and clinical presentation. To date, our understanding of the clinical presentation of CTE is heavily reliant on retrospective interviews with family members of individuals with neuropathologically confirmed CTE. Currently, our neuropathologic understanding of CTE is based on a biased sample of individuals who are who are predominantly among those most exposed to repetitive head impacts (eg. professional football players, professional boxers). What we understand less well is how repetitive head impacts from other less severe and less predictable exposures, such as the occasional concussion or fall, may or may not relate to the development of CTE. However, despite these limitations, there is sufficient scientific evidence to reasonably conclude that CTE is a distinct pathology that is caused, at least in part, by repetitive head impacts.

Our understanding of CTE has progressed considerably in the last several years. However, important gaps still exist in our understanding such as the incidence and prevalence of CIE, nonhead trauma risk factors for the disease, and in vivo diagnostic techniques. There are a variety of factors beyond a history of repetitive head impacts (eg. personality, lifestyle) that differentiate collegiate or professional contact sport athletes from the general public. Understanding to what extent these other factors influence clinical signs and symptoms is critical. Furthermore, there are other non-CTE results of repetitive head impacts. For example, in a 2012 study by Lehman et al. retired NFL athletes were found to have a neurodegenerative mortality rate three-times that of the U.S. population generally, and when AD and amyotrophic lateral sclerosis were examined specifically NFL mortality rates were four times that of the general population [52••]. Differentiating the clinical manifestations of CTE and non-CTE results of head impacts is needed. In order to facilitate clinical understanding of CTE, the most

pressing issue we are faced with is developing an in vivo diagnostic tool. With an in vivo diagnosis, we could begin to directly assess clinical symptomatology and progression, research incidence and prevalence in a living population, and begin therapeutic studies. Without an in vivo diagnosis, the questions we can accurately address are limited by the methodologies we are able to employ.

As CTE research has a particular ability to be misunderstood by the lay public and sensationalized in the media, caution needs to be exercised when discussing results of scientific studies and generalizing the results to the population as a whole. Many individuals have some history of head impacts incurred through sports participation or other activities [53]. However, the pathophysiological mechanism linking this initial trauma, whether concussive or subconcussive, to later-life CTE pathology has yet to be elucidated. Furthermore, without a more complete understanding of the incidence, prevalence, and possible risk factors that lead to the development of CTE, it is impossible for the general population to accurately assess their risk of CTE. Unfortunately the popular media, which has reported on CTE because of its association with professional athletics, often does not present findings with the same accuracy, caution, or contextualization as the original peer-reviewed scientific publications. In order to avoid causing undue panic in individuals who have a history of concussions or other traumatic brain injuries, the scientific community and the media need to clearly address the considerable gaps that exist in our understanding of CIE [54].

Compliance with Ethics Guidelines

Conflict of Interest

Christine M. Baugh and Clifford A. Robbins declare that their institution has received R01 grant support from the NIH. Robert A. Stern declares that his institution has received R01 grant support from the NIH. Dr. Stern also declares the receipt of consulting fees from Athena Diagnostics, as well as gifts to his institution from the National Football League, the Andlinger Foundation, and the NFL Players Association. Dr. Stern also receives royalties from Psychological Assessment Resources, Inc., for psychological tests developed, and he has received consulting fees from law firms in cases involving sports-related brain trauma. Ann C. McKee declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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EXHIBIT 10

Montenigro et al. Alzheimer's Research & Therapy 2014, 6:68 http://alzres.com/content/6/8/68



REVIEW

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

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Abstract

The long-term consequences of repetitive head impacts have been described since the early 20th century. Terms such as punch drunk and dementia pugilistica were first used to describe the clinical syndromes experienced by boxers. A more generic designation, chronic traumatic encephalopathy (CTE), has been employed since the mid-1900s and has been used in recent years to describe a neurodegenerative disease found not just in boxers but in American football players, other contact sport athletes, military veterans, and others with histories of repetitive brain trauma, including concussions and subconcussive trauma. This article reviews the literature of the clinical manifestations of CTE from 202 published cases. The clinical features include impairments in mood (for example, depression and hopelessness), behavior (for example, explosivity and violence), cognition (for example, impaired memory, executive functioning, attention, and dementia), and, less commonly, motor functioning (for example, parkinsonism, ataxia, and dysarthria). We present proposed research criteria for traumatic encephalopathy syndrome (TES) which consist of four variants or subtypes (TES behavioral/mood variant, TES cognitive variant, TES mixed variant, and TES dementia) as well as classifications of 'probable CTE' and 'possible CTE'. These proposed criteria are expected to be modified and updated as new research findings become available. They are not meant to be used for a clinical diagnosis. Rather, they should be viewed as research criteria that can be employed in studies of the underlying causes, risk factors, differential diagnosis, prevention, and treatment of CTE and related disorders.

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by the accumulation of hyperphosphorylated tau protein (p-tau) in neurons and astrocytes in a pattern that is unique from that of other tauopathies, including Alzheimer's disease (AD) and frontotemporal lobar degeneration. The p-tau deposition initially occurs focally, as perivascular neurofibrillary tangles and neurites at the depths of the cerebral sulci. It spreads to involve superficial layers of adjacent cortex, eventually resulting in widespread degeneration of the

medial temporal lobes, frontal lobes, diencephalon, and brainstem [1,2]. Unlike AD, there is a paucity of beta amyloid neuritic plaques. CTE has been found most often in professional athletes involved in contact sports (for example, boxing and American football) who have been subjected to repetitive head blows resulting in concussive and subconcussive trauma [3,4]. Neuropathologically confirmed CTE has been reported in individuals as young as 17 and in athletes who played sports only through high school or college. It also has been found in non-athletes who have experienced repetitive head impacts, including epileptics, developmentally disabled individuals who headbang, and victims of physical abuse [2]. Moreover, CTE has been neuropathologically diagnosed in military service members previously deployed in Iraq and Afghanistan with histories of repetitive brain trauma [2,5]. At this time,

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it is not completely clear whether all cases of neuropathologically confirmed CTE would demonstrate a progressive course if they lived long enough.

All cases of neuropathologically confirmed CTE reported to date have had a history of repetitive head impacts, although there has been some suggestion that a single traumatic brain injury (TBI) may also lead to the neuropathological changes of CTE [6]. Although head impacts appear to be necessary for the initiation of the pathogenetic cascade that eventually leads to neurodegeneration, the history of head impacts is not sufficient and additional risk factors (including genetic susceptibility markers) remain unknown. The incidence and prevalence of CTE are also unknown, although the number potentially affected could be quite large. Every year, between 1.6 and 3.8 million individuals in the US experience a sports-related concussion [7], and the number of youth sports-related concussions has grown in recent years [8]. The incidence of repetitive subconcussive blows (that is, hits to the head that produce enough force to hamper neuronal integrity but that do not result in clinical concussion symptoms) is much greater [9]. For example, a study by Broglio and colleagues [10] found that, per season, high school football players receive an average of 652 head blows that exceed 15 g of force. With over 1 million high school students playing American football each year and with the size and speed of football players increasing [11], the public health impact of CTE may be quite significant in future years.

In vivo diagnosis of CTE is needed to conduct research on risk factors and epidemiology and to perform clinical trials for prevention and treatment. Sensitive and specific biomarkers for CTE are being developed and include structural and neurochemical imaging techniques and positron emission tomography (PET) with new ligands that selectively bind to p-tau [4,12,13]. These approaches hold promise to detect underlying neuropathological changes of CTE. However, the clinical features directly associated with these changes have only recently been described and have been based on retrospective reports of family members of deceased individuals who received a neuropathological diagnosis of CTE [2,14].

In a recent article from our group [14], we examined the clinical presentation of 36 adult males selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy Brain Bank. The cases were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had family member informants who provided retrospective reports of history and clinical features. The semi-structured 'psychological autopsies' were conducted blind to the subjects' neuropathological findings. Three of the 36 subjects were asymptomatic. In the remaining 33 symptomatic subjects, a triad of cognitive, behavioral, and mood impairments was found, and cognitive changes were

reported for almost all subjects at some time in the course of disease. However, two relatively distinct clinical presentations emerged: one group had initial features involving behavior (that is, explosivity, physical and verbal violence, being 'out of control', and impulsivity) or mood (that is, depression and hopelessness) or both (n = 22), and another group had initial features involving cognition (that is, episodic memory impairment, executive dysfunction, poor attention, and concentration) (n = 11). Symptom onset for the 'behavior/mood group' occurred at a significantly younger age than for the 'cognition group'. Most subjects in the behavior/mood group eventually developed cognitive difficulties, although significantly fewer subjects in the cognition group eventually demonstrated behavioral and mood changes. Significantly more subjects in the cognition group developed dementia than those in the behavior/mood group. Less than one third of the sample had reported motor features, including parkinsonism.

Although the study by Stern and colleagues [14] involved the largest case series to date of neuropathologically confirmed cases of CTE without comorbid conditions and with clinical histories, the sample size was small and the generalizability of the findings was hampered by the potential bias of a sample composed of former athletes whose family members agreed to their brain donation. This limitation notwithstanding, the finding of two possible clinical subtypes of CTE was consistent with previous literature. In the present article, we provide a review of the world's literature on the clinical features exhibited by athletes with histories of repetitive head impacts. After the literature review, we provide proposed research diagnostic criteria for 'traumatic encephalopathy syndrome' (TES), derived from this literature review and from our own research into the clinical presentation of CTE [1,2,14]. As described below, these criteria are meant to initially characterize what is known to date and provide a foundation for developing more precise clinical criteria informed by ongoing and future research and clinical review.

Historical terms for chronic traumatic encephalopathy

In his seminal 1928 article in the *Journal of the American Medical Association*, Martland [15] used the term 'punch drunk' to describe boxers suffering from symptoms he believed to be related to the repetitive blows they received in the ring. Since that time, various terms have been used to describe the clinical syndrome associated with repetitive head impacts, predominantly in studies of boxers. In 1934, Parker [16] published an article in which he referred to the 'traumatic encephalopathy of pugilists'. In 1937, Millspaugh [17] first used the term 'dementia pugilistica', which is still used by clinicians and researchers. Other

terms coined through the decades include 'traumatic encephalitis' [18], 'cumulative encephalopathy of the boxer' [19], 'psychopathic deterioration of pugilists' [20], 'chronic boxer's encephalopathy' [21], and 'traumatic boxer's encephalopathy' [22]. In 1949, Critchley first used the designation 'chronic traumatic encephalopathy' [23], or CTE, but later modified it to 'chronic progressive traumatic encephalopathy' [24] because several cases apparently progressed from an early mild state to severe dementia [23-25]. Johnson [26] suggested that the latter term erroneously implies that progression is inevitable. In his case series, little to no deterioration is reported in half of the cases followed for 5 years. In recent reviews of the literature, Victoroff (alone [27] and with Baron [28]) suggested using the more general and inclusive term 'traumatic encephalopathy'.

In 2005, Omalu and colleagues [29] described the first case of neuropathologically confirmed CTE in an American football player. Since that time, there has been increasing public attention to this disease, and reports of CTE in deceased football players, including several well-known athletes, have prompted a tremendous focus on what is commonly referred to as football's 'concussion crisis'. The scientific community also has become dramatically more aware of CTE since it was discovered in American football players. For example, a PubMed search using the terms 'chronic traumatic encephalopathy,' 'traumatic encephalopathy,' 'dementia pugilistica', or 'punch drunk' resulted in 14 publications in the 5-year period ending in December 2001 compared with 116 publications in the 5-year period ending in December 2013.

Early concepts regarding subtypes

In a 1950 editorial in the British Medical Journal, Jokl [30] stressed that CTE was not a single syndrome but rather two kinds of chronic impairment, with either predominant 'behavioral-psychopathic or neurologicalpsychiatric' features. He described the behavioralpsychopathic subtype as involving 'viciousness', 'murder committed from jealousy, and delinquency. In contrast, he described the neurological-psychiatric subtype as involving cognitive deficits, dementia, and motor impairment [30-32]. Grahmann and Ule [33] (1957) described three general subtypes: (1) a progressive dementia that typically involved cognitive impairment and developed following a latency from the time of boxing retirement, (2) a stable neurological presentation temporally and etiologically related to the head impacts and not representative of a progressive disease, and (3) a paranoid and psychotic subtype absent of cognitive changes. Critchley [23] maintained that there were three commonly recurring presentations of CTE that resembled, but could be distinguished from, (1) neurosyphilis (for example, psychopathy, altered personality, and later dementia), (2) multiple sclerosis (for example, scanning speech, tremor, and progressive cognitive decline), and (3) frontal lobe tumor (for example, executive impairments, headache, and eye ache). He later added a fourth presentation: striatal parkinsonian (for example, masked facial features and tremor) [24]. In a study of 17 retired boxers, Johnson [26] described four different 'organic psychosyndromes': cognitive problems with progressive dementia, behavioral issues related to 'morbid jealousy', behavioral issues related to rage and personality disorders, and mood and behavioral disturbance related to persistent psychosis.

Literature search methods

To examine previous literature describing the clinical presentation of CTE associated with exposure to head impacts through sports participation, we conducted a literature search using PubMed, PubMed Central, and Medline databases. Search terms included 'chronic traumatic encephalopathy, 'punch drunk,' traumatic encephalopathy, 'dementia pugilistica,' chronic boxer's encephalopathy, 'chronic progressive traumatic encephalopathy,' 'psychopathic deterioration of pugilists, and 'repetitive brain injury'. In addition, bibliographies of recent literature reviews were cross-referenced [1,27,34-39]. It should be noted that most online databases are limited to articles published since the 1950s. Because essential work in this field began in 1928, archival research was carried out by hand, and international works were obtained with assistance from the Boston University Medical Library Interlibrary Loan Department. Materials retained included articles, reviews, dissertations, society transactions, association reports, and book chapters. To be reasonably confident about the diagnoses used, several criteria were used to determine inclusion in this review: (1) only case series, and not individual case reports, were included; (2) adequate information must be provided in the report to allow classification of cases as confirmed CTE, probable CTE, or possible CTE by using Jordan's criteria [35,40,41]; and (3) only cases involving athletes were included.

Results of literature review

Following the exclusion of articles and cases that did not meet the above criteria, the literature review resulted in 202 cases from 20 published case series, four books, and one medical dissertation. The cases are summarized in Table 1 [2,16,22-26,29,31-33,42-54]. Nineteen cases were published before 1950, 29 cases were published in the 1950s, 49 were published in the 1960s, 13 were published in the 1970s, four were published in the 1980s, 19 were published in the 1990s, and 69 were published since 2000. Using Jordan's criteria [35], we approximated that 29 would have possible CTE, 90 would have probable CTE, and 83 would have definite CTE. Of the entire sample, 141 were boxers, 54 were American football players, five

Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy

		Clinical features			
Study	Sample	Behavioral Mood Cognition			Motor
	(total n = 202)				
Parker [16] (1934)	Boxers (n = 3)	Social	Anxiety	Reduced intelligence	Ataxia
		inappropriateness	Labile emotions	Memory impairment	Clonus
		Childish behavior	Fatigue	Impaired attention	Dragging gait
				Visuospatial difficulties	Dysarthria
					Muscle weaknes
					Spasticity
					Tremor
Herzog [42] (1938)	Boxers $(n = 7)$	Boastfulness	Apathy	General cognitive impairment	Dysarthria
		Personality changes	Flat affect	Memory difficulties	Masked facies
		Impulsiveness		Perseveration	Shuffling gait
		Loss of control		Language difficulties	Truncal ataxia
				Alogia	
				Dementia	
Knoll et al. [43] (1938)	Boxers $(n = 3)$	Personality changes	Apathy	General cognitive impairment	Ataxia
			Flat affect	Memory impairment	Dysarthria
			Loss of interest	Visuospatial difficulties	Masked facies
			Prolix	Alogia	
				Dementia	
Jokl [31] (1941) and Jokl	Boxers $(n = 3)$	Boastfulness	Apathy	Reduced intelligence	Ataxia
and Guttmann [32] (1933)		Childish behavior	Depression	Executive dysfunction	Dysarthria
		Paranoid delusions	Euphoria	Memory impairment	Masked facies
		Personality changes	Fatigue	Impaired attention	Muscle weaknes
		Physical violence	Flat affect	Altered concentration	Shuffling gait
		Psychosis	Insomnia	Language difficulties	Tremor
		Short fuse	Irritability	Dysgraphia	Unsteady gait
		Explosivity	Labile emotions	Visuospatial difficulties	
		Social inappropriateness	Loss of Interest		
		Verbal violence	Mania		
			Mood swings		
Schwarz [44] (1953)	Boxers $(n = 3)$	Personality changes	Fearfulness	Memory impairment	Ataxia
		Short fuse	Irritability	Altered concentration	Dysarthria
		Explosivity	Labile emotions	Language difficulties	Masked facies
					Muscle weaknes
					Stamping gait
					Tremor
					Unsteady Gait
Soeder and Arndt [45] (1954)	Boxers $(n = 5)$	Boastfulness	Apathy	General cognitive impairment	Clonus
		Disinhibited behavior	Depressed mood	Executive dysfunction	Dysarthria
		Inappropriate speech	Euphoria	Memory impairment	Masked facies
		Paranoia	Fatigue	Impaired attention	Rolling gait
		Personality changes	Flat affect	Altered concentration	Tremor
		Physical violence	Insomnia	Language difficulties	Truncal ataxia

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Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy (Continued)

		Psychosis	Mania	Alogia	Unsteady gait
		Short fuse	Mood swings		
		Explosivity	Prolix		
		Social inappropriateness			
Grahmann and	Boxers $(n=4)$	Childish behavior	Apathy	General cognitive impairment	Dysarthria
Ule [33] (1957)	Confirmed CTE (1)	Disinhibited behavior	Depressed	Executive dysfunction	Swaying gait
		Disinhibited speech	Euphoria	Memory impairment	Masked facies
		Impulsivity	Labile emotions	Impaired attention	
		Loss of control	Fatigue	Altered concentration	
		Physical violence	Flat affect	Dementia	
		Personality changes	Irritable		
		Short fuse	Mood swings		
		Explosivity	Prolix		
		Social inappropriateness			
Iuller [46] (1958)	Boxers $(n = 3)$	Social isolation	Fatigue	General cognitive impairment	Dysarthria
		Personality changes	Irritability	Executive dysfunction	Unsteady gait
		Lack of insight		Impaired attention	Spastic gait
				Memory impairment	
				Altered concentration	
				Dementia	
Spillane [47] (1962)	Boxers $(n = 5)$	Childish behavior	Anxiety	General cognitive impairment	Ataxia
		Disinhibited behavior	Depressed mood	Reduced intelligence	Dysarthria
		Impulsivity	Euphoria	Memory impairment	Dragging gait
			Mania	Visuospatial difficulties	Muscle weakne
			Payne mood swings	Dysgraphia	Tremor
				Lack of insight	Unsteady gait
				Dementia	
Mawdsley and	Boxers $(n = 10)$	Impulsivity	Apathy	General cognitive impairment	Ataxia
erguson [22] (1963)		Loss of control	Depression	Reduced intelligence	Dysarthria
		Physical violence	Insomnia	Memory impairment	Dragging gait
		Psychosis	Irritability	Language difficulties	Masked facies
		Paranoid delusions		Dysgraphia	Muscle weakne:
		Personality changes		Dementia	Tremor
		Short fuse			Unsteady gait
		Explosivity			
		Social inappropriateness			
		Verbal violence			
Critchley [23-25] (1949, 1957, 1964)	Boxers (n = 17)	Disinhibited speech	Depressed	General cognitive impairment	Ataxia
	• •••	Disinhibited behavior	Labile emotions	Reduced intelligence	Clumsy
		Impulsivity	Euphoria	Memory impairment	Dysarthria
		Lack of insight	Insomnia	Impaired attention	Masked facies
		Physical violence	Irritable	Altered concentration	Muscle weakne
		Personality changes	Loss of interest	Visuospatial difficulties	Tremor
		Social inappropriateness	Fatigue	Dementia	Unsteady gait
		Short fuse	<u> </u>		/ 3

Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy (Continued)

Payne [48] (1968)	Boxers $(n = 6)$	Disinhibited behavior	Depressed mood	General cognitive impairment	Ataxia
		Impulsivity	Labile emotions	Reduced intelligence	Dysarthria
		Paranoid delusions	Insomnia	Altered concentration	Unsteady gait
		Physical violence	Mania	Visuospatial difficulties	
		Psychotic	Mood swings	Memory impairment	
		Verbal violence	Suicidal ideation		
Johnson [26] (1969)	Boxers $(n = 17)$	Loss of control	Anxiety	General cognitive impairment	Ataxia
		Paranoid delusions	Labile emotions	Reduced intelligence	Dysarthria
		Personality changes	Irritability	Memory impairment	Tremor
		Psychotic		Dementia	Dragging gait
		Short fuse			Masked facies
		Explosivity			Muscle weaknes:
		Verbal violence			
Roberts [49] (1969)	Boxers $(n = 11)$	Lack of insight	Apathy	Reduced intelligence	Ataxia
		Paranoid delusions	Depression	Executive dysfunction	Dysarthria
		Psychosis	Euphoria	Memory impairment	Dragging gait
		Short fuse	Flat affect	Perseveration	Masked facies
		Explosivity	Labile emotions	Impaired attention	Muscle weakness
				Altered concentration	Shuffling gait
				Language difficulties	Spasticity
				Dysgraphia	Tremor
				Visuospatial difficulties	Unsteady gait
				Dementia	
Corsellis <i>et al.</i> [50] (1973)	Boxers $(n = 13)$	Childish behavior	Anxiety	General cognitive impairment	Ataxia
	Confirmed CTE (13)	Paranoid delusions	Labile emotions	Reduced intelligence	Dysarthria
		Personality changes	Irritability	Memory impairment	Masked facies
		Short fuse		Dementia	Muscle weakness
		Explosivity			Tremor
		Social inappropriateness			Staggering gait
		Social isolation			Shuffling gait
		Verbal violence			Unsteady gait
abharwal <i>et al.</i> [51] (1987)	Boxers $(n=4)$	Inappropriate speech	Depression	Reduced intelligence	Ataxia
			Irrîtabîlity	Memory impairment	Spasticity
			Labile emotions		Dysarthria
			Mood swings		
ordan <i>et al</i> . [52] (1997)	Boxers $(n = 19)$	Disinhibited speech	Depression	Impaired attention	Ataxia
		Disinhibited behavior	Irritability	Altered concentration	Clonus
			Flat affect	Memory impairment	Dysarthria
			Mania		Spasticity
					Tremor
					Unsteady gait
Omalu <i>et al.</i> [29,53,54]	Football and	Paranoid delusions	Suicidality	General cognitive impairment	-
2005, 2006, 2010)	wrestling ($n = 5$)	Social isolation	Anxiety	Memory impairment	
		Physical violence	Labile emotions	Language difficulties	
	Confirmed CTE (5)		Irritability	Executive dysfunction	

Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy (Continued)

	•		Insomnia	Impaired attention	
			Depression		
Mckee <i>et al.</i> [2] (2013)	Boxing, American football, ice hockey, wrestling (n = 64)	Explosivity	Depression	Memory Impairment	Dysarthria
		Aggression	Hopelessness	Executive dysfunction	Gait disturbance
		Impulsivity	Suicidality	Impaired attention	Parkinsonism
		Paranola	Mood swings	Language difficulties	
				Visuospatial difficulties	
	Confirmed CTE (64)			Dementia	

CTE, chronic traumatic encephalopathy.

were ice hockey players, and two were professional wrestlers. The clinical features described in all of the cases were classified into one of four categories: behavioral, mood, cognitive, and motor. Table 2 summarizes the clinical features most commonly described across all cases. In 68% of cases, the course of the clinical syndrome was described as progressive. In cases in which a distinction in clinical syndrome was made, the behavioral and mood features were reported to be more stable, whereas the cognitive features were described as progressive, often resulting in dementia. Compared with cases described as progressive, cases described as stable were substantially younger. A large number of cases had a period of latency of several years between the end of exposure to head impacts and the presentation of clinical signs and symptoms. In neuropathologically confirmed cases, authors described the initial clinical presentation as involving mood or behavioral disturbance (or both) without cognitive impairment in 28%, as having cognitive impairment without concurrent mood or behavioral difficulties in 32%, and as having initial mixed cognitive and mood/behavioral disturbance in 40%.

In recent years, some authors have made the distinction between 'classic CTE' and 'modern CTE' [34,36]. For example, McCrory and colleagues [36] define the classic CTE syndrome based on the clinical descriptions from Roberts [49] and the neuropathological reports from Corsellis and colleagues [50]. Based on these earlier cases of boxers, classic CTE is described as having prominent motor features, including gait disturbance, dysarthria, and pyramidal problems, but without progressive cognitive, behavioral, or mood changes [36]. However, it is important to note that, in his monograph, Roberts [49] clarifies that he is intentionally focusing on the description and quantification of motor signs related to

Table 2 Summary of clinical features of chronic traumatic encephalopathy found in the literature

Behavioral features	Mood features	Cognitive features	Motor features	
Explosivity	Depression	Dementia	Ataxia	
Loss of control	Hopelessness	Memory impairment	Dysarthria	
Short fuse	Suicidality	Executive dysfunction	Parkinsonism	
Impulsivity	Anxiety	Lack of insight	Gait Disturbance	
Aggression	Fearfulness	Perseveration	Tremor	
Rage	Irritability	Impaired attention and	Masked facies	
Physical violence	Labile emotions	concentration	Rigidity	
Verbal violence	Apathy	Language difficulties	Muscle weakness	
Inappropriate speech	Loss of interest	Dysgraphia	Spasticity	
Boastfulness	Fatigue	Alogia	Clonus	
Childish behavior	Flat affect	Visuospatial		
Social inappropriateness	Insomnia	difficulties		
Disinhibited speech	Mania	General cognitive impairment		
Disinhibited behavior	Euphoria	Reduced intelligence		
Paranoid delusions	Mood swings			
Personality changes	Prolix			
Psychosis				
Social isolation				

neurological lesions, reducing his focus on 'the evidence of dementia or personality change' which he viewed as occurring in a subset of cases [49]. In contrast, 'modern CTE' [34,36], defined as any case report published in 2005 or later, is characterized by predominant mood and behavioral symptoms as well as later progressive cognitive deficits and dementia but with less prevalent motor features. We view this distinction between the earlier and more recent descriptions of the clinical presentation of CTE as largely an artifact of different sources of trauma exposure (that is, predominantly boxers in the 'classic' cases and predominantly football players in the 'modern' cases).

To explore this issue, we examined further the cases of neuropathologically confirmed pure CTE described in the series of McKee and colleagues [2] and compared the presence of motor features reported for the deceased professional boxers with those reported for the professional football players. The percentage of professional boxers with motor features (71%) far exceeded that of professional football players (13%). Additionally, it was found that in cases with the most advanced stage of CTE neuropathology, there was a striking difference in the presence of cerebellar pathology in professional boxers (83%) and professional football players (57%). The likely cause of this may be related to the differences in the biomechanics of the head trauma that is experienced through the practice of these two different sports [14].

Previously published diagnostic criteria

To date, there have been two published sets of diagnostic criteria for the clinical diagnosis of CTE. The first diagnostic criteria, proposed by Jordan [35,40,41], were developed specifically to represent the likelihood of underlying CTE neuropathology. As such, the following four diagnostic classifications are used: (1) definite CTE ('any neurological process consistent with the clinical presentation of CTE along with pathological confirmation'), (2) probable CTE ('any neurological process characterized by two or more of the following conditions: cognitive and/or behavioral impairment; cerebellar dysfunction; pyramidal tract disease or extrapyramidal disease; clinically distinguishable from any known disease process and consistent with the clinical description of CTE'), (3) possible CTE ('any neurological process that is consistent with the clinical description of CTE but can be potentially explained by other known neurological disorders'), and (4) improbable CTE ('any neurological process that is inconsistent with the clinical description of CTE and can be explained by a pathophysiological process unrelated to brain trauma') [35].

In contrast to Jordan's diagnostic criteria, which are focused on the prediction of underlying CTE neuropathology, the diagnostic criteria of Victoroff [27] are focused on a broad set of clinical signs and symptoms representing a diverse set of possible etiologies and are not meant to predict underlying CTE neuropathology. These provisional research diagnostic criteria for clinically probable traumatic encephalopathy (TE) and clinically possible TE were based on the frequency of clinical symptoms and signs reported in TE case reports published between 1928 and 2010. The Victoroff criteria represent an important addition to the literature but have several limitations. For example, for a diagnosis of clinically probable TE, there is a requirement for two symptoms and three signs. However, there is tremendous overlap and redundancy between the symptoms and the 'neurobehavioral signs,' including the use of the following terms included as both symptoms and signs: memory loss, irritability, apathy, impulsivity, depression, lability, euphoria, paranoia, and others. Another required criterion for clinically probable TE is the 'persistence of both symptoms and signs for at least two years after the traumatic exposure' [27]. This is not consistent with numerous cases of neuropathologically confirmed CTE for which a delayed onset of the clinical presentation is often observed, representing the neurodegenerative nature of the disease [2,14]. An additional limitation to the Victoroff criteria is the lack of any subtyping of the clinical presentation. That is, the same diagnosis of clinically probable TE could be given to an 80-year-old with memory loss, mental slowing, headache, and nystagmus and to a 22-year-old with depression, anxiety, irritability, and anger. This lack of diagnostic subtyping for a condition with such clinically diverse signs and symptoms would reduce the utility of the criteria for research aimed at elucidating specific clinico-pathological relationships or clinical trials requiring greater specificity of diagnosis to ensure meaningful target outcomes. The criteria are presented in a single table without accompanying descriptive prose, making implementation of the criteria potentially subject to individual interpretation. Finally, the Victoroff criteria do not include or recommend the future use of objective diagnostic tests, such as neuroimaging or other potential biomarkers, to improve upon the diagnostic accuracy, specificity, or ability to detect CTE during life.

Proposed research diagnostic criteria for traumatic encephalopathy syndrome

We propose research diagnostic criteria that address many of the limitations of the previously published criteria by Jordan [35,40,41] and Victoroff [27]. These new criteria are derived from the previous literature on CTE reviewed above as well as the specific findings from the studies by Stern and colleagues [14] and McKee and colleagues [2] on the clinical presentation of neuropathologically confirmed cases of CTE. The term 'traumatic encephalopathy syndrome' (TES) was selected instead of 'chronic traumatic encephalopathy' (CTE) for the following reasons:

(1) we view the designation 'CTE' as a neuropathologically defined disease (which is defined by the characteristic deposition of p-tau pathology) rather than a clinical syndrome; (2) TES is meant to describe the clinical presentation of CTE as well as other possible long-term consequences of repetitive head impacts (for example, chronic or progressive axonopathy without tauopathy) but is not meant to include the acute or post-acute manifestations of a single concussion, post-concussion syndrome, or moderate to severe TBI; (3) the use of the word 'chronic' in CTE inaccurately connotes a stable condition rather than a progressive disorder [27]; and (4) the inclusion of the term 'syndrome' appropriately describes the cluster of clinical features that make up this condition. The proposed research diagnostic criteria for TES include five general criteria, three core clinical features, and nine supportive features that are used to define subtypes of TES: a behavioral/mood variant, a cognitive variant, a mixed variant, and TES dementia. The modifiers 'progressive course', 'stable course', and 'unknown/inconsistent course' are used to describe the clinical course, and if specific motor signs are evident, the modifier 'with motor features' is added.

The selection of the five general criteria was based on the literature reviewed above and was designed to favor sensitivity over specificity. This decision is consistent with the previously published diagnostic criteria [27,35] and is appropriate at this early stage of clinical research into this area. To be included as a core clinical feature, the sign or symptom must have been reported in a minimum of 70% of the cases in the study by Stern and colleagues [14] of neuropathologically confirmed cases of pure CTE. This is in contrast to the algorithm employed in the Victoroff [27] diagnostic criteria for which a sign or symptom was included if it was present in at least 7% of the case reports he reviewed from the literature. The nine supportive features were selected to increase specificity once the general criteria are met and are based on features reported in the previous literature.

The clinical diagnosis of TES is not meant to imply a certainty of underlying CTE neuropathological changes (for example, p-tau accumulation). Rather, TES is meant to be a diagnosis of a clinical syndrome associated with a history of repetitive brain trauma. It is expected that some individuals with TES do indeed have CTE neuropathological changes. However, it is also possible that some individuals with TES have other underlying causes of their clinical presentation, including, but not limited to, progressive white matter degeneration [55] or AD. For this reason, a separate diagnostic classification for 'possible CTE', 'probable CTE', and 'unlikely CTE' is included, based on the presence of additional supportive features, such as biomarkers, which indicate the degree to which the underlying etiology of the clinical presentation of TES is likely due to the CTE pathophysiological

process. Finally, we offer six cases (see boxes) as exemplars of the implementation of the TES criteria; each case is a composite of several patients and is created specifically for this purpose.

At this time, risk factors for CTE (above and beyond brain trauma) remain unknown. Among possible variables under investigation by our group and other laboratories are the quantity or severity (or both) of the brain trauma, the initial age and overall duration of head impact exposure, lifestyle factors, and genetic susceptibility. Based on current research findings, it is expected that TES is the clinical manifestation of underlying damage or dysfunction of cortical or subcortical brain structures (or both) and is associated with a history of repetitive brain trauma, including both symptomatic concussions and subconcussive trauma. Although some investigators have suggested that a single moderate to severe TBI may lead to CTE [37] or AD [56] or both, the use of the clinical diagnosis of TES at this time is meant to be used for individuals with repetitive impacts to the head, as defined below. We have included a requirement for a specific minimal amount of exposure to head impacts. This is based on previous findings of post-mortem confirmed CTE cases [1,2,5,50] and will be subject to revisions as additional research is conducted on exposure variables.

General criteria for traumatic encephalopathy syndrome

All five criteria must be met for a diagnosis of TES:

- 1. History of multiple impacts to the head (or to the body resulting in impulsive force transmitted to the head). Multiple impacts are defined based upon (a) the types of injuries and (b) the source of exposure.

 a. Types of injuries:
 - i) Mild TBI or concussion, defined according to the Zurich 2012 Consensus Statement on Concussion in Sport [57] as a 'complex pathophysiological process affecting the brain, induced by biomechanical forces...caused either by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive" force transmitted to the head...the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness'. History of this form of trauma can be based on documented records from health-care providers or on self- or informant-reports, after being given an appropriate definition of 'concussion' [58]. If there is no reported exposure to other

- repetitive hits to the head, there should be a minimum of four documented mild TBIs or concussions.
- ii) Moderate/severe TBI, defined as having loss of consciousness of at least 30 minutes, alteration of consciousness/mental state of more than 24 hours, post-traumatic amnesia of more than 24 hours, and Glasgow Coma Scale score of less than 13 [59]. If there is no reported exposure to other repetitive hits to the head, there should be a minimum of two moderate/severe TBIs.
- iii) 'Subconcussive' trauma, defined as biomechanical force to the head or body similar to, or less than, that required for symptomatic concussion but without symptoms and clinical presentation consistent with concussion [3,4].
- b) Source of exposures:
 - i. Involvement in 'high exposure' contact sports (including, but not limited to, boxing, American football, ice hockey, lacrosse, rugby, wrestling, and soccer) for a minimum of 6 years, including at least 2 years at the college level (or equivalent) or higher.
 - ii. Military service (including, but not limited to, combat exposure to blast and other explosions as well as non-combat exposure to explosives or to combatant or breach training).
 - iii. History of any other significant exposure to repetitive hits to the head (including, but not limited to, domestic abuse, head banging, and vocational activities such as door breaching by police).
 - iv. For moderate/severe TBI, any activity resulting in the injury (for example, motor vehicle accident).
- 2) No other neurological disorder (including chronic residual symptoms from a single TBI or persistent post-concussion syndrome) that likely accounts for all clinical features, although concomitant diagnoses of substance abuse, post-traumatic stress disorder (PTSD), mood/anxiety disorders, or other neurodegenerative diseases (for example, AD and frontotemporal dementia) or a combination of these can be present.
- 3) Clinical features must be present for a minimum of 12 months. However, if treatment (for example, 'antidepressant' medication) results in an improvement in select symptoms, the clinician should use her or his best judgment to decide whether the symptoms would have persisted or progressed if treatment had not been initiated.
- 4) At least one of the core clinical features must be present and should be considered a change from baseline functioning.
- 5) At least two supportive features must be present.

Core clinical features of traumatic encephalopathy syndrome

At least one of the core clinical features must be present:

- 1) Cognitive. Difficulties in cognition:
 - a) as reported by self or informant, by history of treatment, or by clinician's report of decline; and
 - b) substantiated by impairment on standardized mental status or neuropsychological tests of episodic memory, executive function, and/or attention, as defined by scores at a level of at least 1.5 standard deviations below appropriate norms.
- 2) Behavioral. Being described as emotionally explosive (for example, having a 'short fuse' or being 'out of control'), physically violent, and/or verbally violent, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of intermittent explosive disorder would meet this criterion but is not necessary.
- 3) Mood. Feeling overly sad, depressed, and/or hopeless, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of major depressive disorder or persistent depressive disorder would meet this criterion but is not necessary.

Supportive features of traumatic encephalopathy syndrome

A minimum of two of the following features must be present for a diagnosis of TES:

- Impulsivity. Impaired impulse control, as demonstrated by new behaviors, such as excessive gambling, increased or unusual sexual activity, substance abuse, excessive shopping or unusual purchases, or similar activities.
- 2) Anxiety. History of anxious mood, agitation, excessive fears, or obsessive or compulsive behavior (or both), as reported by self or informant, history of treatment, or clinician's report. A formal diagnosis of anxiety disorder would meet this criterion but is not necessary.
- 3) Apathy. Loss of interest in usual activities, loss of motivation and emotions, and/or reduction of voluntary, goal-directed behaviors, as reported by self or informant, history of treatment, or clinician's report.
- 4) *Paranoia*. Delusional beliefs of suspicion, persecution, and/or unwarranted jealousy.
- 5) *Suicidality*. History of suicidal thoughts or attempts, as reported by self or informant, history of treatment, or clinician's report.
- 6) *Headache*. Significant and chronic headache with at least one episode per month for a minimum of 6 months
- 7) *Motor signs*. Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other

- features of parkinsonism. If present, the modifier 'with motor features' should be used (see below).
- 8) Documented decline. Progressive decline in function and/or a progression in symptoms and/or signs, based upon repeated formal testing, clinician examination, or other formal measurement (for example, informant questionnaire) for a minimum of 1 year.
- 9) Delayed onset. Delayed onset of clinical features after significant head impact exposure, usually at least 2 years and in many cases several years after the period of maximal exposure. It should be noted, however, that individual cases may begin to develop the clinical features of TES during their period of head impact exposure (for example, while still actively involved in a collision sport), especially older individuals or those who have been engaged in the high-exposure activity for many years. It may also be difficult to differentiate the clinical presentation of prolonged or persistent post-concussion syndrome (pPCS) from that of TES. Therefore, there could be cases for whom there is overlap of resolving pPCS and the initial features of TES, thus masking any delayed onset of TES.

Traumatic encephalopathy syndrome diagnostic subtypes}

- 1) TES behavioral/mood variant (TES-BMv)
 - a) Behavioral or mood core features (or both) without cognitive core features.
- 2) TES cognitive variant (TES-COGv)
 - a) Cognitive core features without behavioral or mood core features (or both).
- 3) TES mixed variant (TES-MIXv)
 - a) Both cognitive core features and behavioral or mood core features (or both).
- 4) TES dementia (TES-D)
 - a) Progressive course of cognitive core features with or without behavioral or mood core features (or both).
 - b) Evidence of 'functional impairment', defined as cognitive impairment (or cognitive impairment exacerbated by behavioral or mood impairment or both) that is severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living. The determination of functional impairment is based on clinician's judgment, taking into account informant reports as well as consideration of individual differences with regard to level of expected responsibility and daily challenges.
 - c) If the clinical presentation is not distinguishable from that of dementia due to AD or another neurodegenerative disease (for example,

frontotemporal dementia), both diagnoses may be given, either with one being 'primary' and the other being 'secondary' or with the term 'mixed' used if neither is presumed primary.

'With motor features' modifier

For each TES subtype, the modifier 'with motor features' should be added if the individual demonstrates dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism.

Clinical course

For each TES subtype, one of the following additional modifiers should be selected: 'stable course,' to be used when the history or objective testing (or both) indicates that there has been little if any change in symptoms, signs, or other measures; 'progressive course,' to be used when there is a clear indication of progressive worsening of clinical features for at least a 2-year period; and 'unknown/inconsistent course,' to be used when either there is too little information available about the clinical course or the course has been inconsistent, with periods of stability, worsening, and/or improvement. By definition, TES dementia has a progressive course and does not require this modifier.

'Possible CTE' and 'probable CTE'

As stated above, CTE is a neuropathological diagnosis, whereas TES is a clinical diagnosis. As with other neurodegenerative diseases, such as AD, it is not possible at this time to diagnose the underlying disease with certainty during life. However, again as with other neurodegenerative diseases and in keeping with the diagnostic criteria for CTE proposed by Jordan [35,40,41], we propose provisional diagnostic classifications of 'probable CTE', 'possible CTE', and 'unlikely CTE'. Because the scientific study of the clinical presentation of CTE is only in its infancy, it is not yet possible to create meaningful diagnostic criteria for 'probable CTE' based solely on clinical features and course, such as those employed for the National Institute on Aging-Alzheimer's Association (NIA-AA) AD diagnostic criteria for probable AD dementia [60], a condition that has been carefully studied for many decades. Rather, we propose, as a starting point, several potential in vivo biomarkers for CTE that can be used to support a provisional diagnosis of 'probable CTE'. This diagnosis would be analogous to the NIA-AA diagnosis of probable AD dementia with evidence of the AD pathophysiological process [60]. However, because of the early stage of research into potential CTE biomarkers, we refrain from using this type of nomenclature. The following list of potential biomarkers for underlying CTE is meant only as a guideline at this early point in CTE diagnostic research. Many of these biomarkers are the focus of current research but have not yet been

formally validated. Future biomarker validation studies will likely add to or delete (or both) items on this list. Moreover, we do not in any way recommend that the specific tests used for these potential biomarkers be conducted for clinical purposes at this time.

Potential biomarkers for the diagnosis of probable chronic traumatic encephalopathy

- Cavum septum pellucidum. Report of cavum septum pellucidum, cavum vergae, or fenestrations based on neuroimaging study.
- Normal beta amyloid cerebrospinal fluid (CSF) levels.
 CSF beta amyloid levels in the normal range for age and not diminished as would be suggestive of AD.
- 3) *Elevated CSF p-tau/tau ratio*. CSF p-tau/total tau ratio above the normal range for age.
- 4) Negative amyloid imaging. PET amyloid imaging (for example, florbetapir and flutemetamol) in the normal range, not suggestive of AD.
- 5) *Positive tau imaging*. PET paired helical filament tau imaging suggestive of abnormal tau deposition. It should be noted that this remains an experimental procedure and requires additional validation prior to its use as a research tool for diagnostic purposes.
- 6) *Cortical thinning*. Based on magnetic resonance imaging (MRI) measurement, evidence of abnormal cortical thinning indicative of neurodegeneration.
- Cortical atrophy. Based on MRI or computed tomography, generalized cortical atrophy beyond what is expected for age, and, in particular, frontal, thalamic, hippocampal, and/or amygdalar atrophy.

Chronic traumatic encephalopathy classification

- Probable CTE. Meets classification for any TES subtype, progressive course; does not meet diagnostic criteria for another disorder more consistently than TES; and has a minimum of one positive potential biomarker for CTE.
- 2) Possible CTE. Meets classification for any TES subtype, progressive course, and (1) has not undergone any potential biomarker testing, (2) has had negative results on one or more biomarkers with the exception of PET tau imaging (that is, if a negative PET tau imaging finding, the current classification would be 'unlikely CTE'), or (3) meets the diagnostic criteria for another disorder that, on its own, could account for the clinical presentation.
- 3) Unlikely CTE. Does not meet TES diagnostic criteria or has had a negative PET tau imaging scan or both.
- Case A A 45-year-old married man with a history of playing multiple contact sports, including

soccer (ages 5 to 13), hockey (ages 7 to 12), and football (ages 9 to 22) presented to his primary care physician. He played college football at a Division 1 university and was an offensive lineman. He had no reported or formally diagnosed concussions, although when provided with a definition of concussion, he stated that he likely had 20 to 30 throughout high school and college. Since graduating from college, he has worked as an auditor for state government. His work performance evaluations had been routinely positive, although for the past two years they have been marred by reports of 'careless errors,' reduced productivity, and one episode of yelling at his immediate supervisor. His wife of 16 years reports that he has had a 5- to 7-year history of worsening behavior, with frequent episodes of having a 'short fuse' and losing his temper with their two young children. Though always a social drinker, he has had frequent episodes of binge drinking over the past 2 to 3 years. She states that his personality has changed from a kind, even-keeled, loving man to an argumentative, explosive, and moody individual. Both he and his wife state that he was high-functioning, without any cognitive, mood, and behavioral problems during the time period between college and about age 35. He recently underwent formal neuropsychological evaluation that demonstrated moderately impaired sustained attention, mildly impaired delayed recall on a word list, and moderately impaired executive functioning as measured by a card-sorting test. All other areas of functioning were within the normal range. A self-report measure of syndromal depression indicated mild to moderate severity. Other than the recent work-performance evaluations, there were no other reports of significant functional decline. The result of a recent brain MRI was unremarkable other than some mild, scattered white matter abnormalities. Other medical history, laboratory findings, and neurological examination were unremarkable. Diagnosis: TES-MIXv, progressive course; possible CTE. A 31-year-old single female Army veteran was

Case B A 31-year-old single female Army veteran was referred to the VA Medical Center Behavioral Health Clinic for a 14-month history of suicidal thoughts, agitation, and aggressive behavior. She had reached the rank of staff sergeant and was a logistics specialist. She was honorably discharged 1 year ago, began working in her family's grocery store, but had to stop

working 6 months ago because of her neuropsychiatric symptoms. She had two deployments to Afghanistan and denied being directly involved in combat. However, she reported that 20 months prior to her discharge, she was thrown off a truck when it struck an improvised explosive device. She was told she landed on her head and lost consciousness for 2 to 3 minutes. Upon regaining consciousness, she reported 'seeing stars' and had a headache that lasted 3 to 4 days. She denied these symptoms to the medic when questioned and remained on active duty. About 3 months later, a heavy box fell on her head, throwing her to the floor. She denied loss of consciousness but was nauseated and had balance difficulties for several hours. She complained of being in a fog and irritable for 2 days following the accident. Her tour of duty ended 2 weeks later and she returned home. Other than those two injuries, she denied any TBIs or concussions. These symptoms completely cleared, and she described her functioning, including her mood, as 'completely fine' between that time and about 14 months ago. Prior to enlisting, she was an avid ice hockey player, having played since the age of 5, and was the captain of her high school team. Her medical and psychiatric histories were unremarkable, and laboratory results of tests ordered by her primary care physician were normal. At the current evaluation, a mental status examination was conducted and the results were generally within normal limits. She denied having any cognitive complaints. A psychiatric interview revealed significant overall distress, with suicidal ideation without any active plan. Her primary complaints included poor sleep, sadness, anxiety, agitation, and being overly aroused by loud noises. She denied having any flashbacks or night terrors. A sibling was interviewed and corroborated the description and history but added that for the past year she had been verbally aggressive and explosive, frequently yelling at family members for no apparent reason, and that these episodes seemed to turn off and on without any warning. The sibling stated that these abnormal behaviors have been somewhat consistent over the past year. A PTSD specialist examined the patient, reported that she would not meet criteria for PTSD, and questioned whether the symptoms were residual from her TBIs in Afghanistan.

The result of a brain MRI was unremarkable. Diagnosis: TES-BMv, stable course; possible CTE.

Case C A 59-year-old man presented to his primary care physician with complaints of progressive memory and concentration problems. Prior to going to college, the patient entered the Army, where he boxed competitively for 4 years. He did not experience any combat. He was an avid rugby player in college and continued playing in formal competitive clubs until the age of 54, when he stopped because of a cervical disk injury. He received an MBA and had been a successful business consultant. He was divorced at the age of 45 and lived alone. He reported one concussion at the age of 30, when he briefly lost consciousness during a rugby game, although he stated he got his 'bell rung' countless times in boxing and rugby. He reported to his primary care physician that he had been having difficulty remembering details of conversations and meetings at work and that this was beginning to interfere with his productivity. His medical history was significant for the cervical disk injury and for migraine headaches for many years. He was referred to a local academic medical center memory clinic, where a formal neuropsychological evaluation demonstrated moderately impaired performance on a word list recall task, compared with age and education norms, as well as severely impaired fine motor dexterity. All other areas were intact, although his performance on a measure of psychomotor speed and response set maintenance was slightly below expected levels given his history. A neurological examination revealed mild bilateral resting tremor and mild upper extremity rigidity. An MRI scan was read as normal, and all laboratory findings were within normal limits. As part of a clinical research study, he was given two PETs: one with a new tau radiotracer and another with an amyloid tracer. Results indicated no meaningful amyloid uptake, although his tau scan was abnormal with scattered increased tracer uptake in the dorsolateral frontal cortex and the medial temporal lobes. Diagnosis: TES-COGv, with motor features, progressive course; probable CTE.

Case D A 69-year-old former National Football League (NFL) football player was seen in consultation following a 10-year progressive decline. He had seen several physicians and had been given multiple diagnoses, including frontotemporal dementia and dementia due to AD. He had played professional football for 9 years as a linebacker. He began playing football in high school and played for a Division 1 college for 4 years, playing both as a linebacker and as an offensive lineman. Following retirement from the NFL, he had a successful career in commercial real estate until he was forced to retire at the age of 62 because of 'poor decision-making and judgment'. His wife of 25 years stated that, in retrospect, he was demonstrating poor memory and judgment for about 3 years prior to his retirement and that these problems had progressively worsened through the years. She stated that he also began having significant difficulties with multi-tasking and 'numbers' at age 61 and was having difficulty with household finances and hobbies. After retirement, he became increasingly withdrawn and refused to socialize. In contrast to his previous jovial and easy-going manner, he became verbally aggressive toward his wife and children, blowing up over small things'. On two occasions, he became physically aggressive toward his wife, requiring her to call the police. He never demonstrated any disinhibited or socially inappropriate behavior, nor was there any report of hallucinations or movement disturbance. In the past 2 years, his functioning has worsened; he now has no 'short-term memory, watches television all day long, and has an erratic sleep cycle. He is functionally impaired in all instrumental activities of daily living as well as in some basic activities of daily living. His medical history is significant for a myocardial infarction at age 54, hypertension, severe arthritis, and multiple lumbar disk surgeries. There is no family history of dementia. Upon examination, he was disoriented to time and place, was perseverative, and could not recall recent current events. He exhibited some frontal release signs, although the result of his motor examination was otherwise normal. His Mini-Mental Status Exam score was 9, and his Clinical Dementia Rating was 2.0. A neuropsychological evaluation was conducted and demonstrated severe episodic memory impairment as well as profoundly impaired performance on most tests of executive functioning. In contrast, attentional capacity was within normal limits and language was relatively intact. A brain MRI revealed significant global

atrophy with marked hippocampal atrophy as well as a cavum septum pellucidum. An amyloid PET scan demonstrated only minimal uptake, not commensurate with the degree of dementia. Diagnosis: TES-D; probable CTE.

Case E A 31-year-old male stockbroker saw his primary care physician because of an 18-month history of recurrent headaches, irritability, agitation, and a worsening 'short fuse'. He had been taking oxycodone (left over from previous oral surgery) for his headache pain. He was referred to a neurologist, who specialized in headache and who diagnosed him with tension headache. However, when asked if he had ever had headaches previously, the patient reported that he frequently had them as a teenager after his varsity high school football games and when he played rugby for 2 years in college. Because of this history of prior exposure to repetitive head impacts and possible symptomatic concussions, the neurologist referred him to a psychiatrist colleague to evaluate him for possible depression and suicidality, based on the neurologist's belief that the patient might have CTE; he had recently attended a talk on sports injuries. The consulting psychiatrist interviewed the patient, who acknowledged that he had frequent suicidal ideation following the breakup of his marriage about 1 year earlier but that these thoughts had now diminished. Although the patient formally met criteria for TES-BMv, the psychiatrist felt that the headache symptoms, suicidality, short fuse, and irritability were likely associated with the divorce. The patient was prescribed citalopram as well as regular therapeutic massage for his tension headache and was seen in 3 months, at which time he reported substantial improvement of his mood and behavioral symptoms and a complete resolution of his headaches. Diagnosis: adjustment disorder, persistent with mixed anxiety and depressed mood; unlikely CTE. An 81-year-old widowed man enrolled in a research study examining the long-term

anxiety and depressed mood; unlikely CTE.

Case F An 81-year-old widowed man enrolled in a research study examining the long-term consequences of TBI. He reported having sustained a moderate TBI in a motor vehicle accident at the age of 46 with loss of consciousness for approximately 1 hour. He was hospitalized for 3 days because of confusion and memory difficulties that mostly resolved prior to discharge. He was unable to return to work as a high school physical education teacher and coach for several weeks because of continued cognitive difficulties, headache, and

balance problems. He reported that, once he returned to work, he 'didn't feel normal' for several months. He continued working until retirement at age 60. He played high school and college football and reported having had his 'bell rung' 'all the time'. According to his adult son (with whom he lived), he was 72 when he began having memory problems that gradually progressed over the course of 5 to 6 years. In the past few years, the memory problems worsened significantly, such that he could not recall events that occurred more than an hour earlier. In addition, he had worsening problems with judgment, decision-making, multi-tasking, and word-finding. He no longer drove and was dependent in most areas of instrumental activities of daily living. He lacked interest in all activities and appears 'depressed' according to his son. His medical history was significant for prostate cancer, controlled hypertension, arthritis, and glaucoma. Two brothers died in their 80s with 'dementia'. Neuropsychological testing revealed significant impairments in episodic memory, confrontation naming, psychomotor speed, and many aspects of executive functioning, Research-based MRI revealed frontal and temporal atrophy and a pronounced cavum septum pellucidum; diffusion tensor imaging and tractography demonstrated significant reductions in corpus callosum fiber bundles. PET amyloid imaging showed elevated uptake consistent with AD. Diagnosis: dementia due to AD pathophysiological process and TES-D, mixed; possible CTE.

The current proposed research diagnostic criteria for TES are meant to be a starting point that should be modified and updated as new research findings in the field become available and as future research using these criteria are published. These proposed criteria are not meant to be used for a clinical diagnosis or as evidence of an underlying disease. Rather, they should be viewed as research criteria that could be employed in studies of the underlying causes, risk factors, differential diagnosis, prevention, and treatment of TES. Future studies comparing these proposed diagnostic categories with post-mortem neuropathological diagnoses, as well as with appropriate in vivo biomarkers for CTE and other conditions, will help lead to the transition from 'research' criteria to 'clinical' criteria. It also would be critical for these proposed criteria to undergo a formal expert consensus approval process, such as that used for the NIA-AA Diagnostic Guidelines for Alzheimer's Disease [60].

One important factor that must be addressed in future iterations of these criteria is that of base rates. That is, the population prevalence of most of the core clinical features and many of the supplemental features of TES presented below is relatively high. Therefore, it is possible to meet criteria for TES and yet have an idiopathic disorder or a situationally based condition that is unrelated to the earlier history of head impact exposure. The inclusion of supportive features is meant to reduce this lack of specificity to a degree, but, at this time, we acknowledge that these criteria will likely result in very high sensitivity at the expense of specificity. With the utilization of future research findings and subsequent criteria revisions, it is likely that the specificity will increase. An important additional issue regarding the use of these criteria involves the impact of litigation or disability determination (or both) on the validity of symptom reporting and neuropsychological test performance. It is therefore recommended that this issue be taken into account when interpreting the individual's self-reported functioning and test performance and that formal symptom validity checking be conducted as part of any formal evaluation. Until future research yields accurate biomarkers and allows clarification and modification of the proposed criteria, the decision as to whether an individual meets the TES diagnostic criteria and associated 'probable CTE' diagnostic criteria should be left up to the individual researcher, clinician, or, preferably, a multidisciplinary diagnostic adjudication process.

Conclusions

The long-term consequences of repetitive head impacts have been known since the beginning of the 20th century. Although the clinical presentation of CTE is varied and non-specific, there are adequate reports to date to suggest that there may be two clinical subtypes: one subtype involving primarily behavioral or mood features (including explosivity or violence) or both, and the other involving cognitive deficits (including impairments in episodic memory, executive functioning, and attention). Many individuals progress to dementia, with impaired functional independence, and some individuals develop motor impairments (including parkinsonism, ataxia, and dysarthria). We propose research diagnostic criteria for TES that we hope will facilitate research into this area. There are expected limitations to the development of diagnostic criteria based primarily on a relatively small number of case reports. The goal of proposing these criteria at this time is to facilitate research in this nascent area of study. It is expected that these criteria will undergo modification and revision as new research findings become available, additional biomarkers are validated, and future research using these criteria are published.

Note: This article is part of a series on *Traumatic brain injury*, edited by Robert Stern. Other articles in this series can be found at http://alzres.com/series/traumaticbraininjury

Abbreviations

AD: Alzheimer's disease; CSF: Cerebrospinal fluid; CTE: Chronic traumatic encephalopathy; MRI: Magnetic resonance imaging; NFL: National Football League; NIA-AA: National Institute on Aging-Alzheimer's Association; PET: Positron emission tomography; pPCS: Persistent post-concussion syndrome; p-tau: Phosphorylated tau; PTSD: Post-traumatic stress disorder; TBI: Traumatic brain injury; TE: Traumatic encephalopathy; TES: Traumatic encephalopathy syndrome behavioral/mood variant; TES-DGv. Traumatic encephalopathy syndrome cognitive variant; TES-D: traumatic encephalopathy syndrome dementia; TES-MIXV: Traumatic encephalopathy syndrome dementia;

Competing interests

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EXHIBIT 11

Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma

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KEYWORDS

- Encephalopathy, Post-traumatic
- Neurodegenerative disorders Concussion Athletic injuries
- Dementia
 Motor neuron disease

It has been understood for decades that certain sporting activities may increase an athlete's risk of developing a neurodegenerative disease later in life. Not surprisingly, this association was originally noted in boxers, athletes who receive numerous blows to the head during training and competition. In 1928, Harrison Martland, a New Jersey pathologist and medical examiner, first described the clinical spectrum of abnormalities found in "nearly one half of the fighters who have stayed in the game long enough." 1

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Boxers exhibiting cognitive, behavioral, or motor abnormalities were well known to lay persons, sportswriters, and others within the boxing community and were referred to by various terms, such as "punch drunk," "goofy," and "slug-nutty"^{2,3}; later, the more formal term *dementia pugilistica* was introduced to lend medical validity to the condition. By the 1970s, a sufficient number of boxers with dementia pugilistica had been studied pathologically to support the conclusion that this form of neurodegeneration was similar to, but distinguishable from, other causes of neurodegenerative disease. As evidence of the clinical and neuropathologic consequences of repeated mild head trauma grew, it became clear that this pattern of neurodegeneration was not restricted to boxers, and the term chronic traumatic encephalopathy (CTE), originally coined by Miller⁶ became most widely used.

Over the last several decades, clinical and neuropathologic evidence of CTE has emerged in association with various sports, including American football, professional wrestling, professional hockey, and soccer, as well as other activities associated with repetitive mild head trauma, such as physical abuse, epileptic seizures, and head banging.⁷⁻¹³ Although the incidence and prevalence of CTE is currently unclear, it probably varies by sport, position, duration of exposure, and age at the time of initial or subsequent head trauma, and with additional variables, such as genetic predisposition. To date, there have been no randomized neuropathologic studies of CTE in deceased athletes, and as such, there is a selection bias in the cases that have come to autopsy. If one considers the prevalence in deceased professional American football players who died between February 2008 and June 2010, there were 321 known player deaths¹⁴ and the brains of 12 of the 321 underwent postmortem neuropathologic examination at Boston University Center for the Study of Traumatic Encephalopathy (BU CSTE), All 12 examined neuropathologically showed evidence of CTE, suggesting an estimated lifetime prevalence of at least 3.7%. If one assumes that all deceased players who did not come to autopsy did not have CTE and that the amount of head trauma in professional football has remained fairly constant over the past 5 decades, a prevalence of 3.7% would result. Although this represents a conservative estimate, it suggests a significant public-health risk for persons who suffer repetitive mild traumatic brain injury (TBI).

CLINICAL SIGNS AND SYMPTOMS OF CTE

Whereas concussion and postconcussion syndrome represent temporary states of neuronal and axonal derangement, CTE is a neurodegenerative disease that occurs years or decades after recovery from the acute or postacute effects of head trauma. The exact relationship between concussion and CTE is not entirely clear, although repetitive axonal perturbation may initiate a series of metabolic, ionic, membrane, and cytoskeletal disturbances, which trigger the pathologic cascade that leads to CTE in susceptible individuals. 15,16 The onset of CTE is often in midlife, usually after athletes have retired from their sport. In some individuals, the early manifestations of CTE affect behavior; in particular, individuals with neuropathologically documented CTE have been described by family and friends as being more irritable, angry, or apathetic or as having a shorter fuse. Increased suicidality seems to be a particularly salient symptom of CTE. 17 In other cases, cognitive difficulties may be the first signs to emerge, with poor episodic memory and executive functioning being two of the most common cognitive dysfunctions reported. Later in the disease, movement (eg, parkinsonism), speech, and ocular abnormalities may emerge in the context of declining cognition and worsening comportment. A minority of cases with neuropathologically documented CTE developed dementia before death; the relative infrequency of

dementia in individuals with CTE may be due in part to many individuals with CTE having committed suicide or died from accidents or drug overdose at an early age. 11,17

NEUROPATHOLOGY OF CTE Gross Pathology

Neuropathologic studies of athletes with a history of repeated mild head injuries have produced several consistent findings that, together, make CTE a distinctive disorder. On gross examination, there is often anterior cavum septi pellucidi and, usually, posterior fenestrations. These changes may be caused by the force of the head impact being transmitted through the ventricular system, thereby affecting the integrity of the intervening tissue. Enlargement of the lateral and third ventricles is also commonly seen in CTE; the third ventricle may be disproportionately widened. Additional gross features include atrophy of the frontal and temporal cortices and of the medial temporal lobe, thinning of the hypothalamic floor, shrinkage of the mammillary bodies, pallor of the substantia nigra, and hippocampal sclerosis. Atrophy of the cerebrum, diencephalon, basal ganglia, brainstem, and cerebellum may result in an overall reduction in brain mass.¹¹

Microscopic Neuropathology

Tau

Microscopically, CTE is characterized by an abundance of neurofibrillary inclusions in the form of neurofibrillary tangles (NFTs), neuropil threads (NTs), and glial tangles (GTs). The main protein composing NFTs is the microtubule-associated protein tau, and NFTs are aggregates of filamentous tau polymers. Although CTE shares many microscopic similarities with Alzheimer disease (AD) and other tauopathies, it has several distinguishing features. First, the distribution of tau pathology is unique; it is most commonly found in the more superficial cortical laminae (II and III), whereas tau NFTs in AD are preferentially distributed in large projection neurons in layers III and V. Further, the regional tau pathology is extremely irregular, largely confined to uneven foci in the frontal, temporal, and insular cortices, unlike the more uniform cortical NFT distribution seen in AD. Tau NFTs, NTs, and GTs are found throughout the medial temporal lobe, often in densities greater than those found in severe AD, and are also prominent in the diencephalon, basal ganglia, and brainstem. NTs and GTs are also found in the subcortical white matter. Finally, NFTs in CTE are most dense at the depths of cortical sulci, and are typically perivascular, which might indicate that disruptions of the cerebral microvasculature and the blood brain barrier that occur at the time of the traumatic injury play a critical role in the formation of NFTs. 11

Although the precise pathologic mechanisms that tie repeated mild head injuries to NFT formation are not known, they may involve a series of diffuse axonal injuries (DAI) set in motion by the initial trauma and aggravated by subsequent mild traumatic injuries. During a TBI, the brain and spinal cord undergo shear deformation producing a transient elongation or stretch of axons. Traumatic axonal injury results in alterations in axonal membrane permeability, ionic shifts including massive influx of calcium, and release of caspases and calpains that might trigger tau phosphorylation, misfolding, truncation, and aggregation, as well as breakdown of the cytoskeleton with dissolution of microtubules and neurofilaments.^{15,18,19}

Increasing evidence indicates that tau phosphorylation, truncation, aggregation, and polymerization into filaments represents a toxic gain of function, and continued accumulation of tau leads to neurodegeneration. This is supported by tau's involvement in some genetic forms of frontotemporal degeneration²⁰ and by work that shows

that plasmids containing human tau complementary DNA constructs microinjected into lamprey neurons in situ produce tau filaments that accumulate and lead to neuronal degeneration. However, it is also possible that the intracellular NFTs, by themselves, are the byproducts rather than the cause of cellular injury and that NFT formation indicates neurons that survived the initial injury and sequestered the abnormally phosphorylated, truncated, and folded tau. A possible tau toxic factor or transcellular propagation by the misfolded tau protein may explain how a neurodegeneration that starts multifocally around small blood vessels or in the depths of cortical sulci ultimately spreads to involve large regions of brain as a systemic degeneration, such as CTE. A

Beta-amyloid

Beta-amyloid (Aβ) deposits are found in 40% to 45% of individuals with CTE, in contrast to the extensive $A\beta$ deposits that characterize nearly all cases of AD. Although neuritic plaques are typically abundant in AD and are essential to the diagnosis, Aß plagues in CTE, when they occur, are less dense and predominantly diffuse. 11 Despite the fairly minor role A β plaques seem to play in the neuropathologic manifestation of CTE, the role of A β in the pathogenesis of CTE has yet to be elucidated. It is known that acute head injuries cause an upregulation of amyloid precursor protein (APP) production and that Aβ plaques may be found in up to 30% of patients who die within hours of TBI.^{25–27} DAI, often a consequence of mild TBI, is thought to influence changes in Aß after head injury. Interruption of axonal transport causes an accumulation of multiple proteins in the axon, including APP, in varicosities along the length of the axon or at disconnected axon terminals, termed axonal bulbs.²⁸ Although the axonal pathology in TBI is diffuse in that it affects widespread regions of the brain, typically, the axonal swellings are found in multifocal regions of the subcortical and deep white matter, including the brainstem. Because of the rapid and abundant accumulation of APP in damaged axons after TBI, APP immunostaining is used for the pathologic assessment of DAI in humans. Accordingly, this large reservoir of APP in injured axons might be aberrantly cleaved to rapidly form Aβ after TBI.^{25,29,30} However, it remains unclear whether the large quantities of APP and Aβ found in damaged axons after TBI play any mechanistic role in neurodegeneration or neuroprotection. 28,31,32 Moreover, it is unknown how long the increased APP and Aβ lasts or what mechanisms may result in variable clearance.

TDP-43

Recently, in addition to severe tau neurofibrillary pathology, the authors found a wide-spread TDP-43 proteinopathy in more than 80% of their cases of CTE. ¹³ Moreover, in 3 athletes with CTE who developed a progressive motor neuron disease several years before death, there were extensive TDP-43 immunoreactive inclusions in the anterior horns of the spinal cord, along with tau-immunoreactive GTs, neurites, and, occasionally, extensive NFTs. These findings suggest that a distinctive, widespread TDP-43 proteinopathy is also associated with CTE and that, in some individuals, the TDP-43 proteinopathy extends to involve the spinal cord and is clinically manifest as motor neuron disease with a presentation that may appear similar to amyotrophic lateral sclerosis (ALS). ¹³ The shared presence of 2 aggregated phosphorylated proteins associated with neurodegeneration in the great majority of cases of CTE suggests that a common stimulus, such as repetitive axonal injury, provokes the pathologic accumulation of both proteins. ³³ Recent studies in vitro and in vivo suggest that over-expression of wild-type human TDP-43 and its dislocation from the neuronal nucleus to the cytoplasm are associated with neurodegeneration and cell death. ^{34–36} By virtue

of its capacity to bind to neurofilament messenger RNA (mRNA) and stabilize the mRNA transcript, TDP-43 plays a critical role in mediating the response of the neuronal cytoskeleton to axonal injury. TDP-43 is intrinsically prone to aggregation, and its expression is upregulated after experimental axotomy in spinal motor neurons of the mouse.³⁷ Traumatic axonal injury may also accelerate TDP-43 accumulation. aggregation, and dislocation to the cytoplasm, thereby enhancing its neurotoxicity.

CLINICAL IMPLICATIONS

CTE is a Potential Late Effect of Repeated Head Injuries

CTE is not thought to be a long-term sequela after a specific head trauma. Rather, its clinical symptoms emerge later in life, usually after athletes retire from their sport. Like most other neurodegenerative diseases that cause dementia, CTE has an insidious onset and gradual course. Based on a recent review of neuropathologically confirmed CTE in athletes¹¹, the mean age at onset is 42.8 years (SD = 12.7; range = 25-76vears). On average, onset occurs approximately 8 years after retirement (SD = 10.7), although approximately one-third of athletes were reportedly symptomatic at the time of retirement. In athletes, the course seems to be considerably protracted (mean duration = 17.5 years, SD = 12.1), especially in boxers. The average duration of the disease in boxers is 20 years (SD = 11.7) and 6 years in American football players (SD = 2.9).¹¹ If the affected individual does not die of other causes, full-blown clinical dementia may occur late in the course of the disease.

Diagnosis of CTE

Currently, the clinical diagnosis of CTE is difficult because there are no consensus diagnostic criteria or large-scale longitudinal clinicopathologic correlation studies. The differential diagnosis of CTE often includes AD38 and frontotemporal dementia (FTD)³⁹, depending on the age at onset and the presenting problem. Older individuals with memory difficulties may seem to have AD, and, in fact, may have evidence of AD and CTE neuropathologically. 11 When the age at onset is earlier (eq. 40s or 50s) and the patient presents with behavioral dysregulation or apathy, it may be difficult to rule out FTD. Although a history of remote head trauma may be suggestive of CTE, head trauma has been implicated as a risk factor of AD, Parkinson disease, ALS, and other neurodegenerative diseases. 40-42 Therefore, without neuropathologic confirmation, currently, a clinical diagnosis of CTE cannot be made with a high degree of confidence. Furthermore, the clinical phenotype of CTE may be confounded by alcohol or other drug abuse. Several individuals with neuropathologically confirmed CTE are thought to have developed problems with drug abuse as a consequence of the loss of inhibitory control caused by the neurodegenerative disease. From a clinical perspective, however, it can be difficult to determine whether the drug abuse problems are a cause of symptoms or simply one of many ways in which CTE is manifested.

Although the neuropathologic features of CTE seem to be distinct from other neurodegenerative diseases, no currently agreed neuropathologic criteria exist for the diagnosis of CTE. Once established, these criteria can be applied at autopsy in large-scale, prospective longitudinal studies of athletes with a history of repetitive head injuries. Establishing neuropathologic diagnostic criteria would allow for the identification of clinical criteria and biomarkers to improve the accuracy of CTE diagnosis in the living.

Several biomarkers are believed to have the potential to contribute to identifying CTE in vivo. For instance, the changes to white-matter integrity caused by repeated head trauma may be amenable to detection using diffusion tensor magnetic resonance imaging. 43 Magnetic resonance spectroscopy may be capable of detecting changes in glutamate/glutamine, N-acetyl aspartate, and myo-inositol, molecular abnormalities that may serve as markers of brain damage caused by head injuries. 44 Further, measuring tau and phospho-tau in cerebrospinal fluid may yield diagnostically useful markers of CTE. 45

Risk and Protective Factors

CTE research is in its infancy, and decades of research are probably necessary to achieve CTE diagnosis early in its course using a combination of clinical tools and biomarkers. However, the research already conducted has profound implications for current practice by medical professionals, athletic trainers, and related specialists, as well as policy makers in government and athletic organizations. CTE is the only known neurodegenerative dementia with a specific identifiable cause; in this case, head trauma. It is unknown whether a single blow to the head is sufficient to initiate the metabolic cascade that precedes the clinical and neuropathologic changes characteristic of CTE, because all confirmed cases of CTE to date have had a history of multiple head injuries. Therefore, the most obvious way to prevent CTE is, in theory, to prevent repetitive head injuries from occurring. In some sports, such as boxing and American football, it may be impossible to prevent repetitive head injuries, especially the repeated subconcussive blows that are characteristic of the impacts felt by offensive and defensive linemen in football on nearly every play. For sports in which repeated blows to the head are unavoidable, proper concussion assessment and management may be paramount for preventing long-term consequences. Currently, it is unknown whether returning to play while symptomatic from a previous concussion or sustaining a second concussion while symptomatic is a risk factor of developing CTE. However, other strategies to reduce the number and severity of head traumas are possible, such as limiting full-contact practices, implementing rules of play that diminish the likelihood of repeated head trauma (eg, removing the 3-point stance in football), or increasing the use of newer protective headgear aimed at absorbing force, thus diminishing the impact to the brain.

Along these lines, many potential variables surrounding head trauma in athletes may be important for preventing CTE later in life. The sport played and the position played within each sport may be relevant; for instance, boxers receive a greater proportion of rotational forces to the head, whereas American football players receive a greater proportion of linear forces to the head. Even within the same sport, athlete exposure to head injuries can differ considerably. In American football, some positions, such as wide receiver, may receive occasional severe blows with the potential to cause unconsciousness, whereas other players, such as linemen, may take hundreds of small impacts per season, most of which are not, by themselves, forceful enough to cause symptoms. It is unknown whether CTE is more likely to occur after a small number of severe head injuries, a large number of subconcussive injuries, or other forms of head trauma. Currently, investigations are ongoing that attempt to quantify the force of head impacts across different sports and positions. These findings will play an important role in understanding the specific head injury variables that influence CTE risk.

The age at which athletes suffer their head injuries may also influence CTE risk. At younger ages, the brain may be more vulnerable to injury. ⁴⁹ Conversely, the increased plasticity of the young brain may be better able to compensate for specific difficulties, such as behavioral dysfunction. ⁵⁰ It is also not clear whether particular lifestyle factors may be protective against CTE in the context of repetitive head injuries. In other neuro-degenerative diseases such as AD, the neuropathology is thought to precede the clinical symptoms, possibly by several decades. ⁵¹ The same may be true of CTE, as

evidenced by the presence of CTE neuropathology in asymptomatic individuals studied at autopsy. Conceivably, health and medical factors that are absent or present during this preclinical stage may influence the extent of neurodegeneration or the brain's ability to compensate for any neurodegeneration. For instance, the presence of chronic inflammation, as in that which accompanies medical conditions such as obesity, hypertension, diabetes mellitus, atherosclerosis, and heart disease, may facilitate neurodegeneration and NFT formation, 52-55 Also, as with other neurodegenerative diseases like AD, some individuals may have greater cognitive reserve, thus increasing the threshold for the clinical manifestation of the underlying neuropathologic condition.

Genetic variations may also play an important role in moderating the relationships between head trauma, neuropathologic changes, and disordered cognition and behavior. One of the genes thought to influence CTE risk is the apolipoprotein E (APOE) gene. The APOE ε4 allele, important in the genetics of AD, may also increase the risk of CTE. Based on genetic testing conducted in conjunction with neuropathologic examinations of individuals with a history of repeated head injuries, approximately 57% of individuals with neuropathologically confirmed CTE possessed at least one APOE ε4 allele. When contrasted with the estimated 28% of the population possessing at least one APOE ε4 allele, 56 the frequency of this allele in those with CTE seems higher than expected. This genetic link is currently speculative, because formal epidemiologic studies have yet to be conducted. However, individuals carrying the APOE ε4 allele may be more likely to have a poor outcome after TBI, especially in individuals younger than 15 years. 57-59 Epidemiologic data have also implicated the APOE ε4 genotype as a risk factor for the development of AD after TBI, 60,61 and carriers of the APOE ε4 allele were found to be at increased risk of Aβ deposition after TBI.⁶²

SUMMARY

CTE is a neurodegenerative disease that occurs later in the lives of some individuals with a history of repeated head trauma. The exact relationship between repetitive mild TBI, with or without symptomatic concussion, and CTE is not entirely clear, although it is possible that repetitive axonal injury sets up a series of metabolic, ionic, and cytoskeletal disturbances that trigger a pathologic cascade, leading to CTE in susceptible individuals. CTE has been reported in association with American football, professional wrestling, soccer, and hockey, as well as in association with physical abuse, epilepsy, and head banging behaviors, suggesting that mild TBI of diverse origin is capable of instigating CTE. CTE often manifests in midlife and produces clinical symptoms of disordered cognition, memory loss and executive dysfunction, depression, apathy, disinhibition, and irritability, as well as parkinsonian signs. The characteristic neuropathologic features of CTE include extensive tau-immunoreactive inclusions scattered throughout the cerebral cortex in a patchy, superficial distribution, with focal epicenters at the depths of sulci and around the cerebral vasculature and widespread TDP-43-immunoreactive inclusions that may occasionally be associated with symptoms of motor neuron disease. Currently, neuropathologic examination of brain tissue is the only way to diagnose CTE, although intense research efforts are underway to identify biomarkers to detect the disease and monitor its progression and to develop therapies to slow or reverse its course. Longitudinal research efforts are underway to shed additional light on the specific variables related to head trauma, neuropathology, and clinical presentation of CTE that remain in question.

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EXHIBIT 12

Neurology®

Clinical presentation of chronic traumatic encephalopathy

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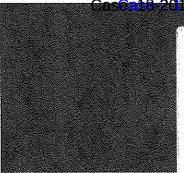


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Clinical presentation of chronic traumatic encephalopathy

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AB

ABSTRACT

Objective: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

Methods: Thirty-six adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank. Subjects were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had next-of-kin informants to provide retrospective reports of the subjects' histories and clinical presentations. These interviews were conducted blind to the subjects' neuropathologic findings.

Results: A triad of cognitive, behavioral, and mood impairments was common overall, with cognitive deficits reported for almost all subjects. Three subjects were asymptomatic at the time of death. Consistent with earlier case reports of boxers, 2 relatively distinct clinical presentations emerged, with one group whose initial features developed at a younger age and involved behavioral and/or mood disturbance (n = 22), and another group whose initial presentation developed at an older age and involved cognitive impairment (n = 11).

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavior/mood variant and the other a cognitive variant. Neurology® 2013;81:1122-1129

GLOSSARY

AD = Alzheimer disease; CSTE = Center for the Study of Traumatic Encephalopathy; CTE = chronic traumatic encephalopathy; p-tau = hyperphosphorylated tau; RBT = repetitive brain trauma; TBI = traumatic brain injury,

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease marked by widespread accumulation of hyperphosphorylated tau (p-tau). ^{1,2} To date, CTE has been documented in amateur and professional athletes involved in contact sports, military personnel exposed to explosive blast, and others subjected to repetitive brain trauma (RBT), including concussive and subconcussive injuries. ^{1–5} All reported neuropathologically confirmed cases of CTE have had exposure to RBT. However, not all individuals with histories of RBT develop CTE, indicating that additional risk factors, including genetics, likely have a role in the neuropathogenesis of this disease. For example, it has been suggested that the *APOE* E4 allele may increase susceptibility for CTE.⁶

Previously published descriptions of the clinical presentation of CTE vary. Case reports of presumptive CTE (formerly termed dementia pugilistica or "punch-drunk" when thought limited to boxers⁴) indicated a constellation of clinical features, including impairments in cognition, behavior, and mood, and in some cases, chronic headache and motor and cerebellar dysfunction. Several case reports of boxers suggested 2 forms of presentation: 1) younger onset, with initial behavioral and mood disturbance, but with minimal cognitive and motor features; and 2) older onset, with greater cognitive impairment and, often, motor disturbance. ^{4,7–10} In advanced cases,

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CTE is associated with dementia, although it is unclear whether the clinical presentation of CTE dementia is different from that associated with Alzheimer disease (AD) or other age-related neurodegenerative disorders. ^{11–13} Herein, we describe the clinical presentation, course, and *APOE* genotype of a sample of 36 athletes with neuropathologically confirmed CTE.

METHODS Subjects. The brains of 81 subjects in the Boston University Center for the Study of Traumatic Encephalopathy (CSTE) brain bank met recently published criteria for the neuropathologic diagnosis of CTE.\(^1\) For the current study, 45 cases were excluded because of 1) primary exposure to RBT from non-athletic activities; 2) inability to contact next-of-kin to conduct an interview; and 3) presence of comorbid motor neuron disease,\(^1\) neurodegenerative disease, or other significant neuropathology. Seven were military veterans with unknown or no athletic history, 10 had no next-of-kin contact, and 28 had comorbid neuropathologic disease. Of the 36 remaining subjects, 28 were included in a previous report\(^1\) and 8 were new cases.

CTE neuropathologic staging. The cases were categorized into the 4-stage rating scale of CTE (I = least severe, IV = most severe) based on the severity of p-tau pathology, as previously reported. Diagnosis and staging were conducted blind to medical history, *APOE* genotype, and informant interview.

Interview and medical record review. History and clinical presentation were obtained through postmortem telephone interviews with next-of-kin by a neuropsychologist (R.A.S.) blinded to neuropathologic findings and APOE genotype status. Medical records were available and reviewed for 23 cases. The semistructured interview was based on previous studies of postmortem dementia diagnosis made by interviews with family members. 15,16 Information queried during the interview included the following: demographics; cause of death; and athletic, military, medical, neuropsychiatric, and social/occupational histories. The interview included specific questions regarding dementia, depression, changes in cognition, behavior, mood, and motor functioning, as well as instrumental activities of daily living. Responses were qualitatively summarized into an overall assessment of the subject's presentation and course of symptoms and functioning. The number of informants interviewed per case ranged from 1 to 7 (median = 2), with each interview lasting approximately 60 minutes. Interviews were conducted at a median time of 4 months after time of death.

APOE genotyping. DNA was extracted from brain tissue samples using a Qiagen QIAamp DNA extraction kit (Qiagen, Valencia, CA). Two single nucleotide polymorphisms (National Center for Biotechnology Information SNPs rs429358 and rs7412) were examined using TaqMan assays (Applied Biosystems, Foster City, CA). Allelic discrimination was automated using the manufacturer's software. Positive controls, consisting of DNA of each of the 6 possible APOE genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4), were included on each plate and genotyped with restriction isotyping.

Statistical analyses. Between-group differences were examined by independent sample *t* tests. Chi-square analyses were used for between group comparisons for categorical data. *APOE* genotype analyses comparing CTE cases with population norms¹⁷ were

conducted with the χ^2 goodness-of-fit test. A probability level of p=0.05 was used throughout. All statistical analyses were conducted with IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY).

Standard protocol approvals, registrations, and patient consents. Approvals for brain donation, postmortem clinical record review, interviews with family members, and neuropathologic evaluation were provided by the Institutional Review Boards of Boston University Medical Center and the Bedford VA Hospital.

RESULTS Table 1 summarizes the demographics, cause of death, athletic history, neuropathologic stage, and APOE genotypes of the sample. All subjects were male athletes, with 6 (17%) African American and 1 (3%) of Hispanic origin. There were 29 football players (22 who played professionally, 4 who only played through college, and 3 who only played through high school), 3 professional hockey players, 1 professional wrestler, and 3 boxers (1 professional, 2 amateur). Of the football players, the most common position played was lineman (48%), followed by running back (21%), linebacker (10%), and smaller numbers of other positions. There were no quarterbacks or kickers. Of the 36 subjects, 3 (8%) were asymptomatic. Tables 2 and 3 describe the clinical features and course of the remaining 33 subjects.

Eleven of the symptomatic cases were reported to have initial changes in cognitive functioning (e.g., episodic memory impairment, executive dysfunction) before behavioral or mood disturbance. Initial changes in behavior (e.g., explosivity, impulsivity, violence) before mood or cognitive disturbance were reported in 13 subjects. Mood changes (e.g., depression, hopelessness) were reported as the initial feature in 9 subjects. None of the subjects had motor disturbance as their initial feature. The subgroups with initial behavioral symptoms and mood changes were similar in age of initial presentation, age of death, and neuropathologic stage, and were combined into a behavior/mood group (n = 22). Subjects whose initial difficulties involved cognitive functioning comprised a cognition group (n = 11). Tables 1-3describe demographics and clinical features for the behavior/mood and cognition subgroups.

Ten subjects were diagnosed with dementia; 4 were clinically diagnosed with AD, 4 with "dementia pugilistica" or "football-related" dementia, and 2 with unspecified dementia. All had stage IV CTE. Of the 10, 7 exhibited cognitive symptoms initially, 2 exhibited mood symptoms initially, and 1 initially presented with behavior changes. The mean age of symptom onset for the dementia group was 57.7 years (SD = 18.3; range 25–82) and the mean age of dementia diagnosis was 72.6 years (SD = 8.5, range 56–83). The mean length of time between dementia diagnosis and death was 8.0 years (SD = 5.5, range <1–15). Four subjects with dementia had gait difficulties, 3 had

Table 1 Description of sample by initial clinic	cal presentation		
Variable	All subjects (n = 36)	Behavior/mood group (n = 22)*	Cognition group (n = 11)*
Age at death, y, mean ± SD (range)	56.8 ± 21.9 (17-98)	51,4 ± 18,5 (21-84) ^b	69.2 ± 21.8 (34-98) ^b
Cause of death, %			
Systemic illness	41,8	49.8	27.3
Accidental overdose	13.9	18.2	91
Dementia-related	13,9	9.1	27,3
Suicide Fill History Control of the Suicide Fill History Control o	16,7	18,2	18.2
Injury	8.4	4.5	18.2
Years of education, mean ± SD (range)	15.0 ± 2.4 (10-20)	14.5 ± 2.4 (10-18)	15.7 ± 1.4 (13-18)
Football as primary sport, %	80,6	72,7	90,9
Total years of football played, mean ± SD (range)	15,3 ± 6,4 (3-25)	14.4 ± 6.5 (3-25)	18,2 ± 5,9 (5-24)
Neuropathologic severity stage, %		and the second s	
· · · · · · · · · · · · · · · · · · ·	7 8	91	0
Stage II	28	31.8	9.1
製 Stage III : 1 : 1 : 1 : 1 : 1 : 1 : 1 : 1 : 1	31	31.8	36,4
Stage IV	33	27.3	54.5
APOE genotype, %			
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:3/:3	63	63.6	54.5
	26	27,3	27.3
# 14/4 # 10 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5			18.2

^{*}Three subjects were asymptomatic; percentages within initial feature group are based on the percent of symptomatic subjects.

a history of falls, and 1 had a history of tremor. Two subjects (20%) with dementia had a history of headaches, compared with 11 subjects (44%) without dementia. All 10 subjects had both memory and executive impairment, 7 had language deficits, and 2 had visuospatial difficulties. Six of the 10 were characterized by behavioral impairment, predominantly described as having a "short fuse" or being "out of control." Four of the 10 were physically violent and 2 were verbally violent. Although one subject demonstrated disinhibited behavior, none of the subjects had disinhibited speech or socially inappropriate behaviors. Of the 7 who were reported to have mood disturbance, 2 had predominantly sadness/depressive symptoms and 2 had anxiety symptoms. The only 2 subjects in the entire sample reported to have had apathy were in the dementia group.

The proportions of *APOE* genotypes (i.e., $\epsilon 4$ homozygotes, combined $\epsilon 4$ homozygotes and heterozygotes, and $\epsilon 4$ noncarriers) in our CTE sample were significantly different from those found in an age-matched normative sample¹⁷ (χ^2 [2] = 6.63, ρ < 0.05). A

binomial test revealed that the primary difference between our CTE sample and population norms was a greater proportion of $\varepsilon 4$ homozygotes in our sample (p < 0.05). When examining the 2 initial presentation groups, there were no differences between the behavior/mood group and the age-matched normative sample $(\chi^2 \ [2] = 0.46, p > 0.05)$. However, there were proportionally more $\varepsilon 4$ homozygotes in the cognition group than expected $(\chi^2 \ [2] = 13.3, p < 0.05)$. The relative proportions of APOE genotypes in our 10 subjects with dementia were not significantly different from those seen in AD¹⁸ $(\chi^2 \ [2] = 1.52, p > 0.05)$.

DISCUSSION Consistent with earlier reports of boxers, 4.7–10 our findings suggest that there may be 2 different clinical presentations of CTE, with one initially exhibiting behavioral or mood changes, and the other initially exhibiting cognitive impairment. The behavior/mood group demonstrated symptoms at a significantly younger age than the cognition group. Although almost all subjects in the behavior/

^bStatistically significant between-group difference, p < 0.05.

^{*}One subject did not have APOE genotyping,

Table 2 Clinical features and course by in	itial clinical presentation	i	
Variable	All symptomatic subjects (n = 33)*	Behavior/mood group (n = 22)*	Cognition group (n = 11)*
Percent with progressive course	90.9	86,4	100
Percent with dementia diagnosis at death	30.3	18,2 ⁶	54.5 ⁶
Age first clinical feature observed, y, mean ± SD (range)	42.5 = 17.8 (19-82)	34.5 ± 11.6 (19 - 59) ⁶	58.5 ± 17.7 (31+82) ^b
Duration of clinical features, y, mean ± SD (range)	14.9 ± 12.9 (0-51)	17.0 ± 14.3 (0-51)	10.7 ± 8.5 (1-30)
Initial clinical domain, %		·	
Cognition	33.3		100
Behavior	39,4	59,1	
Mood Table 1	27,3	40,9	
Clinical domain(s) ever observed during life, %			
Cognition	93,9	90.9	100
Behavior	75.8	86.4 ^b	54.5 ^b
Mood	84.8	95.4 ^b	63,6 ^b
Motor	30.3	27.3	36.4
Cognition and behavior	75.8	86.4	54.5
Cognition and mood	81.8	90.9	63,6
Cognition and motor	30,3	27.3	36,4
Behavior and mood	72.7	86.4	45.5
Behavior and motor	27.3	27.3	27.3
Mood and motor	30,3	27,3	36,4
Cognition, behavior, and mood	72,7	86.4	45,5
Cognition, behavior, and motor	27.3	27.3	27.3
Cognition, mood, and meter	30.3	27.3	36.4
Behavior, mood, and motor	27,3	27,3	27,3
All 4 domains	27.3	27,3	27,3
History of significant headaches, %	34.4	38.1	27.3
Death by suicids, %	18.2	182	18.2
History of substance abuse, %	39,4	36,4	45,5

^{*}Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.

mood group demonstrated cognitive impairments at some point, significantly fewer subjects in the cognition group demonstrated behavioral and mood changes during the course of their illness. There were distinctions between the 2 groups regarding specific features present in each domain. The behavior/mood group was significantly more explosive, out of control, physically and verbally violent, and depressed than the cognition group. Whereas all subjects in the cognition group were reported to have impaired episodic memory, approximately one-quarter of the behavior/mood group did not have memory difficulties. Subjects in the cognition group were significantly more likely to progress to dementia than those in the behavior/mood group but were also significantly older at the time of death. Given the small sample size in this study, however, it is unclear whether these 2 apparently distinct clinical subtypes are representative of all individuals with CTE. In addition, the subsample of cases with dementia is also small, thus limiting the generalization of the presentation of CTE dementia. Further research is needed to clarify and validate these findings.

We examined the potential role of the APOE & allele as a susceptibility factor for CTE. Our findings indicate that there were significantly more & 4 homozygotes in the sample than expected in a normal, agematched population. Furthermore, this effect was largely driven by the cognition group: 2 of 11 subjects in the cognition group and 1 of 22 subjects in the behavior/mood group were homozygous for the & allele. In addition, 1 of the 10 CTE subjects diagnosed

^bStatistically significant, p < 0.05.

Variable	All symptomatic subjects, % (n = 33)	Behavior/mood group, % (n = 22)*	Cognition group, % (n = 11)*
Cognitive features			
Memory impairment	84,8	77.3	100
Executive dysfunction	78.8	72.7	90.9
Attention and concentration difficulties	72.7	63.6	90.9
Language impairment	57.6	54.5	63,6
Visuospatial difficulties	54.5	54.5	54.5
Behavioral features			
Explosivity	57,6	72,7"	27,3
Impulse control problems	45.5	54.5	27.3
"Out of control"	51.5	63.6 ^b	27.3°
Physically violent	51,5	68.2 ^b	18,2 ^h
Verbally violent	48.5	73.6 ^b	18,2 ^b
Disinhibited speech	O	0	0
DisInhibited behavior	3.0	0	9.1
Socially inappropriate	3.0	O	9,1
Paranola	18.2	22.7	9,1
Mood features	7.		
Sadness/depression	63.6	86.4 ^b	18.2 ^b
Anxiety/agitation	15,2	13,6	18,2
Manic behavior/mania	3,0	4,5	0
Suicidal ideation/attempts	30.3	31,8	27.3
Hopelessness	63.6	72.7	45.5
Apathy	6.1	9.1	O

^a Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.

with dementia during life was \$4 homozygous. Although interpretation and generalization of these results is difficult because of the small sample, the proportion of £4 homozygosity is in contrast to population norms in which £4 homozygosity only occurs in 1% to 3% of the general population,17 and more consistent with the 10% of patients with AD who are £4 homozygous.18 The APOE E4 variant is the largest known genetic risk factor for sporadic AD.18 It has been associated with B-amyloid, but not tau, deposition in cognitively normal aging.19 APOE E4 has also been associated with greater severity of cognitive deficits and longer recovery time after traumatic brain injury (TBI) and RBT in a variety of populations, including boxers and professional football players,20-24 and may increase the risk of clinical dementia after TBL25 It has been hypothesized that the APOE E4 isoform may have direct neurotoxic effects leading to mitochondrial dysfunction and cytoskeletal changes, resulting in increased risk of neurodegeneration.²⁶ Despite the small sample size and other limitations in the current study, future research on the role of APOE in CTE risk appears warranted. However, other potential susceptibility genes also merit consideration, including mutations to the microtubule-associated protein tau (MAPT) gene, the progranulin (GRN) gene, and the chromosome 9 open reading frame 72 (C9ORF72) gene. Moreover, additional nongenetic risk factors for CTE should be examined in future research, including studies to determine what specific aspects of RBT exposure (e.g., types, severity, frequency, initial age, and duration of trauma) are associated with CTE, as well as what potential lifestyle variables (e.g., diet, exercise, obesity, steroid use) are associated with the disease initiation and variability in presentation.

It is noteworthy that motor features, including parkinsonism, were not common in our sample. This is in contrast to some earlier descriptions of CTE in boxers, in which these motor features were quite prominent.4 However, our findings are consistent with other case reports of predominantly younger onset boxers, in which motor disturbance was not common. 4.7-10 It is not clear why some individuals with CTE develop motor features and others do not. One possibility may be the differences in the biomechanics of injury. For example, in boxing, angular acceleration and torsional injury involving the brainstem and cerebellum is thought to be a pathogenic mechanism of TBI after a hook or jab to the jaw, whereas transverse and linear acceleration and deceleration injury are more characteristic of football dynamics.^{27,28} As a result, degeneration of brainstem structures that produce parkinsonism, such as the substantia nigra, might occur earlier in the course of disease in boxers. In contrast, football players might develop substantia nigra degeneration later in the course of their disease, at a time when widespread cortical and basal ganglionic degeneration mask the development of motor disturbance. Related mechanisms of injury leading to CTE have been suggested by recent experimental studies of blast neurotrauma.3

Although many of the symptoms of CTE are similar to AD and other causes of dementia, 11,29 there are factors that appear to clinically differentiate CTE from other age-related neurodegenerative diseases. For example, behavioral changes observed early in the course of CTE could be confused with the behavioral variant of frontotemporal dementia, especially in a patient in his or her 50s without any significant memory impairment. However, common changes in the behavioral variant of frontotemporal dementia typically include disinhibited and inappropriate behavior and speech, as well as apathy³⁰; these symptoms were not frequent in our case series. In addition, the progressive memory impairment observed in more than 80% of our CTE cases, and in all 10 of

^bStatistically significant between-group difference, p < 0.05.

the subjects with dementia, could lead to an inaccurate diagnosis of AD when the underlying disease is CTE. 12

It is not clear what neuropathologic changes may lead to the 2 possible clinical presentations observed in this study. It is unlikely that the small, focal cortical p-tau lesions found in stage I and II CTE produce clinically meaningful behavioral and mood symptoms. However, these features may be associated with the neurofibrillary tangles in the locus coeruleus and amygdala found in younger subjects in a previous report.1 The memory and executive dysfunction in the older cognition group may be due to the more extensive degenerative changes in the hippocampus and frontal cortices seen in CTE stages III and IV.1 It is possible, however, that some of the features evident in the younger behavior/mood group were due to persistent postconcussion syndrome,31 with unresolved or even progressive³² axonal damage resulting from the initial traumas. Axonal injury has been shown in all neuropathologic stages of CTE, ranging from multifocal, perivascular axonal varicosities in the cortex and white matter in stages I and II, to more extensive, diffuse axonal loss in the cortex and white matter in stages III and IV.1 Recent reports have demonstrated that repetitive subconcussive trauma is associated with white matter abnormalities on diffusion tensor imaging^{33,34} and abnormal functional MRI tests.35 Additional findings indicate that there may be persistent and progressive inflammation and white matter degeneration after even a single TBI.36 Further research is required to delineate these clinicopathologic relationships.

Three subjects in our case series were asymptomatic. One of these cases was only 17 years old and had stage I neuropathology. Both of the other 2 cases were much older football players (one in 40s, one in 80s), had stage II neuropathology, and were homozygous for APOE E3. Both also had advanced graduate degrees, were very successful in their professional careers, and were described as extremely intelligent. Although speculative, these findings raise the possibility that cognitive reserve³⁷ may have a role in protecting against the clinical manifestations of CTE. A recent report suggests that cognitive reserve may mitigate cognitive decline in older individuals with earlier life TBI.38 Future research examining the roles of cognitive reserve, genetics, and environmental factors in determining resilience to clinical manifestations and the progression of p-tau pathology will help elucidate the pathobiology of CTE.

Although these findings are based on the largest cohort of subjects with neuropathologically confirmed CTE without comorbidities studied to date, interpretation and generalizability of these results are limited by several factors. First, the overall sample

size is small, and caution should be taken when generalizing these results to the larger population of athletes or to the overall clinical presentation of CTE. In addition, there are inherent selection biases imposed in a postmortem brain donation study. For example, families choosing to donate may be more likely to have witnessed symptoms during life. This could lead to reports of more severe symptoms than a typical CTE population, and could account for only having 3 asymptomatic cases. From the broader CTE cohort in the CSTE brain bank, we selected a smaller sample by eliminating individuals with comorbid pathology and only including athletes; this restriction may further limit the generalizability of our findings. Results from this study should not be interpreted in terms of population prevalence or generalized to living athletes with CTE. In addition, there is the potential for reduced reliability and validity of retrospective reports from family members after the death of a loved one. However, several studies have demonstrated adequate reliability and validity of these verbal autopsies in a variety of patient populations, including those with dementia^{15,16} and psychiatric disorders.³⁹ There also may be differences in the accuracy of informant reports when comparing younger and older subjects. That is, informants of older subjects were asked to recall early- or midlife events possibly resulting in reduced accuracy compared with the informants of younger subjects. Finally, there was no comparison group of former athletes without CTE. This may limit the ability to draw conclusions that the clinical presentation described is specifically due to the effects of CTE. In our available dataset of subjects whose tissue had been examined at the BU CSTE brain bank, there was not an adequate number of subjects without CTE to make such a comparison. For example, 34 of 35 former professional football players had neuropathologically confirmed CTE.1 Future research is needed to clarify the clinical presentation of CTE. The development of biomarkers (e.g., blood, CSF, neuroimaging, and tau-specific radiotracers) will result in the ability to detect and diagnose CTE during life and subsequent studies of risk factors, epidemiology, and treatment.40

AUTHOR CONTRIBUTIONS

Dr. Stem was responsible for drafting the manuscript, study concept and design, and analysis and interpretation of data. He also conducted some of the statistical analyses and had a role in obtaining funding. Mr. Daneshvar participated in drafting the manuscript, as well as acquisition of data, statistical analysis, and interpretation of data. Ms. Baugh participated in drafting the manuscript, as well as study design and acquisition of data. Dr. Seichepine participated in drafting the manuscript, as well as analysis and interpretation of data. Mr. Montenigro participated in drafting the manuscript and in study design. Mt. Riley participated in revising the manuscript, study design, and acquisition of data. Mr. Pritts, Ms. Stamm, Mr. Robbins, and Ms. McHale participated in revising the manuscript and acquisition of data. Ms. Simkin participated in revising the manuscript as well as conducting the APOE genotyping. Dr. Stein and Dr. Alvarez participated in revising the

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manuscript, as well as acquisition and analysis of neuropathologic data. Dr. Goldsrein and Dr. Budson participated in revising the manuscript and interpreting the data. Dr. Kowall participated in revising the manuscript, interpreting the data, and obtaining funding. Mr. Nowinski participated in revising the manuscript, study concept, acquisition of data, and obtaining funding. Dr. Cantu participated in drafting the manuscript, study design and concept, interpreting data, and obtaining funding. Dr. McKee participated in drafting the manuscript, study design and concept, acquiring, analyzing, and interpreting clinical data, acquiring, analyzing, and interpreting the neuropathologic data, and obtaining funding.

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DISCLOSURE

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This Week's Neurology® Podcast



The complexities of acute stroke decision-making (See p. 1130)

This podcast opens and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the September 24, 2013, issue of *Neurology*. In the second segment, Dr. Brett Kissela talks with Dr. Michel Shamy about his paper on the complexities of acute stroke decision-making. Next, Dr. Roy Strowd reads our e-Pearl of the week about Adie's tonic pupil. Then, Dr. Brett Kissela focuses his interview with Dr. Lou Caplan on his medical education and contributions to the field of neurology, interactions with C. Miller Fisher, and advice to our younger listen-

ers beginning their careers. Disclosures can be found at www.neurology.org.

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EXHIBIT 13



Written Testimony of Robert A. Stern, Ph.D.

Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology
Director, Clinical Core, BU Alzheimer's Disease Center
Co-Founder, Center for the Study of Traumatic Encephalopathy
Boston University School of Medicine

Before the Special Committee on Aging United States Senate

Hearing on "State of Play: Brain Injuries and Diseases of Aging"

Wednesday, June 25, 2014

Special Committee on Aging United States Senate June 25, 2014

Good afternoon, Mr. Chairman, Ranking Member Collins, and distinguished Members of the Committee. It is a great honor to appear before you today for this hearing on "Brain Injuries and Diseases of Aging." My name is Dr. Robert Stern. I am a Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology at Boston University School of Medicine. I am also the Director of the Clinical Core of the Boston University (BU) Alzheimer's Disease Center, one of 29 Alzheimer's research centers funded by the National Institute on Aging. In 2008, I cofounded the BU Center for the Study of Traumatic Encephalopathy (now referred to as the BU CTE Center) with Dr. Ann McKee, Dr. Robert Cantu, and Mr. Christopher Nowinski who is also testifying before you today.

For the past 25 years I have been conducting clinical neuroscience research, primarily focused on the cognitive, mood, and behavioral changes of aging, in general, and in neurodegenerative diseases, in particular. I have been on the faculties of the University of North Carolina School of Medicine, Brown Medical School, and, for the past 10 years, Boston University School of Medicine. In my role in the BU Alzheimer's Disease Center, I oversee all clinical research pertaining to Alzheimer's disease (AD), including studies aimed at the diagnosis, genetics, prevention, and treatment of this devastating disease.

Chronic Traumatic Encephalopathy (CTE)

Since 2008, my research has focused on the long-term consequences of repetitive brain trauma in athletes. In particular, I have been studying the neurodegenerative disease, chronic traumatic encephalopathy or CTE. CTE is a progressive neurodegenerative disease that can lead to dramatic changes in mood, behavior, and cognition, eventually leading to dementia. It is similar to AD but is a unique disease, easily distinguished from AD and other diseases through post-mortem neuropathological examination. CTE has been found in individuals from ages 16-98, including youth, college, and professional contact sport athletes (including football, hockey, soccer, and rugby players), military service members exposed to blast trauma and other brain injuries, and others with a history of repetitive brain trauma, such as physically abused women, developmentally disabled head bangers, and seizure disorder patients. (See **Table 1.**)

Although CTE has been known to affect boxers since the 1920s (previously referred to as "punch drunk" or dementia pugilistica), it is only recently—since CTE was diagnosed in several deceased former professional NFL players—that this disease has received greater medical <u>and</u> media attention. However, the scientific knowledge of CTE is in its infancy. The little that is known is based primarily on post-mortem examinations of brain tissue and interviews from the family members of the deceased athletes. What these studies have shown

is that, in some individuals, early repetitive brain trauma triggers a cascade of events in the brain leading to progressive destruction of the brain tissue. The hallmark feature of CTE is the build-up of an abnormal protein called tau (See **Figure**; based on the work of Dr. McKee), one of the abnormal proteins also seen in AD (McKee et al., 2013). These changes in the brain can begin years, or even decades, after the last brain trauma or end of athletic involvement, and can lead to memory loss, poor judgment, impulse control problems, aggression, depression, suicidality, movement problems, and, eventually, progressive dementia (See **Table 2**).

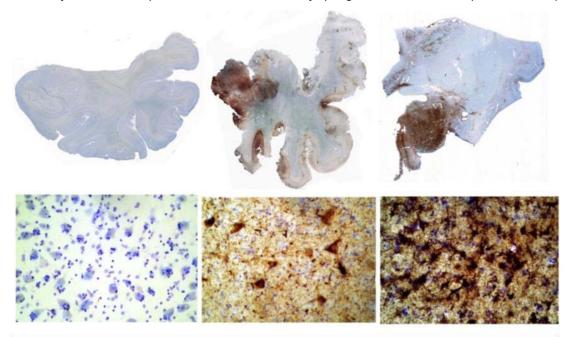


Figure of CTE Neuropathology. Left Top: Section of brain of 65 year old healthy man demonstrating no evidence of abnormal tau depositions. Left Bottom: Microscopic enhancement of same brain sample demonstrating no evidence of tau neurofibrillary tangles that would have shown up as brown from immunostain. Middle Top: Section of brain from 45 year old John Grimsley, a former NFL football player who had a five year decline in functioning (e.g., poor memory, short fuse) prior to his death from an accidental gunshot wound; brown areas are abnormal tau deposits. Middle Bottom: Microscopic enhancement of Grimsley's brain demonstrating neurofibrillary tangles. Right Top: Section of brain of 73 year old former professional boxer who died in a nursing home with clinical diagnosis of dementia pugilistica after several year decline in functioning; brown areas demonstrate widespread tau deposition. Right Bottom: microscopic enhancement of boxer's brain demonstrating widespread tau deposits

The Symptoms of CTE

Although the cognitive changes in CTE are very similar to those in AD, many individuals with CTE develop the significant changes in mood and behavior relatively early in life (Stern, et al., 2013) that can lead to significant distress for the individual with CTE as well as their family, friends, and other loved ones. These mood and behavioral impairments caused by CTE are typically misdiagnosed and attributed to routine psychiatric disorders, stress, substance abuse, or pre-existing personality traits. However, it is completely expected that the areas of the brain

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damaged in CTE would lead to these problems, including depression, impulsivity, emotional lability, irritability, and behavioral dyscontrol. It is noteworthy that the much heralded "NFL Settlement" (currently in limbo while the judge examines several issues) began as a class action to address the issue of CTE in former NFL players and to provide the players and their families with appropriate compensation for the losses and distress experienced due to CTE. However, the "settlement," as it is currently written, does not provide <u>any</u> compensation for individuals with the mood and/or behavioral impairments so common in CTE. For example, the families of well-known former players who died of suicide and were found to have CTE post-mortem, such as Junior Seau and Dave Duerson, would not receive any benefits under the currently written settlement if they died after the acceptance of the settlement. Rather, only individuals with the memory, cognitive, and functional independence difficulties associated with Alzheimer's disease dementia would meet criteria for compensation.

Table 1. All cases of neuropathologically confirmed cases of CTE have had a history of repetitive brain trauma. CTE has been diagnosed in the following individuals:

Professional football players

College football players

High school football and other contact sport athletes

Professional soccer players

Semiprofessional soccer player

Professional rugby players

Boxers

Mixed martial art athlete

Combat military service members

Others, including a domestically abused woman, seizure disorder patients, developmentally disabled headbanger

Like other neurodegenerative diseases, CTE can only be diagnosed through post-mortem neuropathological examination of brain tissue. Dr. Ann McKee from our BU center has examined the brains of more athletes and others with repetitive brain trauma than any other neuropathologist. As part of the investigation of these postmortem cases, I have had the great privilege and honor to interview the family members of approximately 100 deceased former athletes who were diagnosed with CTE after death by Dr. McKee and her team. From these interviews I have begun

to learn about the clinical course and presentation of this disease. But, more importantly, I have learned about the tremendous pain and suffering the family members experienced while their loved one's life was destroyed by the progressive destruction of the brain. I have spoken with spouses of former professional football players who slowly lost their ability learn new information, communicate with others, dress, feed, and toilet themselves. I have interviewed

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the adult children of former professional and college football and rugby players whose fathers had dramatic changes in personality, the development of aggressive and out-of-control behavior, and suicidal thoughts. And, I have spoken with the parents of young athletes in their 20's or 30's who impulsively took their own lives.

Table 2. Clinical Features of Chronic Traumatic Encephalopathy			
Behavioral Features	Mood Features	Cognitive Features	Motor Features
Explosivity	Depression	Memory impairment	Ataxia
Loss of control	Hopelessness	Executive dysfunction	Dysarthria
Short fuse	Suicidality	Lack of insight	Parkinsonism
Aggression and rage	Anxiety	Perseveration	Gait Disturbance
Impulsivity	Irritability	Impaired attention	Tremor
Physical/verbal	Labile emotions	and concentration	Masked facies
violence	Apathy	Language difficulties	Rigidity
Paranoid delusions	Loss of interest	Dementia	Muscle weakness

Diagnosing CTE During Life

I also have been privileged to meet over 70 former NFL players who have come to Boston to participate in my NIH-funded research study entitled, *Diagnosing and Evaluating* Traumatic Encephalopathy with Clinical Tests, or DETECT. I hear their histories, I speak with their family members, and I listen to their fears that they have CTE or that their fellow former football players have or will get CTE. They have all witnessed firsthand the tragic downward spiral of CTE that sadly seems to have become an expected consequence of playing the game they loved. The goal of the DETECT study (which was the first grant ever funded by NIH to study CTE) is to develop objective biological tests, or biomarkers, in order to detect and diagnose CTE during life. The study involves the examination of a total of 100 former professional football players (selected based on positions played and existing clinical symptoms) and 50 same-age non-contact sport elite athletes. All research participants undergo extensive brain scans, lumbar punctures (to measure proteins in cerebrospinal fluid), electrophysiological studies, blood tests (e.g., for genetic studies and novel potential biomarkers), and in-depth neurological, neuropsychological, and psychiatric evaluations. In addition, I have recently received Department of Defense funding (with my colleague, Dr. Martha Shenton of the Brigham and Women's Hospital) and a separate grant from Avid Radiopharmaceuticals (part of Ely Lily) to examine an exciting new Positron Emission Tomography (PET) ligand (developed and owned by Avid) that is specifically designed to attach to the abnormal forms of tau protein found in CTE. Preliminary results of the DETECT study are very promising. However, it is just the first step. Future research is needed, including

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longitudinal designs with much larger samples and the inclusion of newer techniques and technologies, as well as post-mortem validation of the findings during life.

To me, the ability to diagnose CTE during life is the next critical step in the study of CTE. It will lead to the ability to answer important questions about this disease, such as: How common is CTE? What are the risk factors for CTE? Can it be prevented? How can we treat it? In other words, at this point, we actually know very little about this disease (See Table 3). One thing we do know about CTE is that every case of post-mortem diagnosed CTE has had one thing in common: a history of repetitive brain trauma. This means that the repetitive brain trauma is a necessary factor in developing this disease. However, it is not a sufficient factor. That is, not everyone who hits their head repeatedly will develop this progressive brain disease. There are additional, as yet unknown, variables that lead to CTE, such as genetic susceptibility or specific aspects of the exposure to the brain trauma. Some have argued that brain trauma cannot possibly cause CTE, using the argument that there are many older former football players and other athletes with dramatic brain trauma history who are completely healthy. This irrational argument is analogous to those made years ago that cigarette smoking does not cause lung cancer because there are many people who smoked for decades who never develop lung cancer. An important next step in CTE research is to examine the specific additional risk factors, including genetics and exposure variables.

Subconcussive Trauma

It is important to note that CTE is not a disease restricted to former *professional* athletes. It has been found in individuals who only played their sport up through the *college* level and even just through *high school*. It has been found in warfighters who were exposed to blast trauma and other injuries. Another important issue to note is that post-mortem confirmed CTE has been found in individuals who have had <u>no</u> history of known or reported symptomatic concussions, but, nonetheless, were exposed to a tremendous amount of repetitive hits to the head that did not result in the symptoms of concussion. These "subconcussive" blows are quite common. It is estimated that the typical lineman in football experiences between 1000-1500 hits per season (i.e., at every snap of the ball at every play of every game and every practice), each at 20-30*g*. These hits are not just experienced by professional players. For example, a study by Broglio and colleagues (2011) found that high school football players received, on average, 652 hits to the head in excess of 15*g* of force in a single season. One player received 2,235 hits! To put this in perspective, a car going 35 mph into a brick wall experiences approximately 20*g* of force. There is now growing research evidence that even after one season, repetitive

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subconcussive trauma can lead to cognitive, physiological, and structural changes to the brain. And, it appears that this exposure to repetitive subconcussive blows is associated with the development of CTE. This, perhaps, is one of the most frightening aspects of CTE. Over the past few years, there has been a tremendous increase in public awareness of *concussions* and the need to prevent and manage them. The "concussion crisis" in sports is a hot topic in the media, on playing fields, and in doctor's offices. However, when it comes to the long-term consequences of sports-related brain trauma, <u>concussions are likely the tip of the iceberg</u>. That is, subconcussive trauma appears to be as important or more important in the development of CTE.

Table 3. CTE Research is in its Infancy: What are the Important Questions to Address?

How common is CTE?

Is it a critical public health issue?

Above and beyond having a history of repetitive brain trauma, what are the risk factors for CTE?

Do genetics play a role in determining who gets CTE?

What types of brain trauma exposure increase risk?

Is there a certain age in childhood or adolescence when the brain is more vulnerable to brain trauma, increasing CTE risk?

How can we diagnose CTE during life?

Are there specific biomarkers that can accurately detect the abnormal tau deposition in the brain during life?

Can we distinguish between Alzheimer's disease and CTE by clinical examination?

How can we treat the symptoms of CTE effectively?

Can we modify the disease course if we intervene early?

Can CTE be prevented?

What is the biological mechanism for the development of CTE?

How does the abnormal tau move from one part of the brain to another?

Increased Funding for CTE Research

In order to tackle the complex issue of CTE, we must expand upon current approaches to conducting research in neurodegenerative disease. We must break down the traditional silos of individual research labs, research institutions, and disciplines, and begin to conduct multidisciplinary, collaborative research across research centers, bringing together the very best scientists, novel methodologies, and state-of-the-art technology. Most importantly, we must not forget that our research must focus on reducing individual human suffering and improving public health. Alas, this requires tremendous financial support. And, as you all know, current NIH funding is tragically low. The budget cuts to NIH in recent years have resulted in a tragic slowdown in the momentum of scientific discovery, and have led many scientists — both young

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investigators and older senior researchers – to leave their careers in the biomedical sciences. A recent survey by the *Chronicles of Higher Education* (Baskin & Vossen, 2014) of 11,000 senior researchers found that almost half of the respondents already abandoned an area of scientific investigation they considered key to their lab's mission. And more than three-quarters had reduced or eliminated their recruitment of graduate students and post-doctoral fellows because of reduced funding.

I want to express my deepest gratitude toward this Committee and its members for leading the recent effort to increase NIH funding of Alzheimer's disease research. However, we must have additional funding to support research focusing on CTE and the long-term consequences of repetitive brain trauma in athletes, military service members, and other members of society. In addition to direct federal funding, this effort will require public-private collaborative funding, such as that which supported the revolutionary Alzheimer's Disease Neuroimaging Initiative or ADNI. What might come as a surprise is that in 2012, the National Football League (NFL) donated \$30 million to the Foundation for NIH to support peer-reviewed research studies on injuries affecting athletes, with brain trauma being the primary area of focus. However, that is just the beginning. We need much, much more.

In summary, many of our most cherished games in our country, such as football, hockey, and soccer, often involve repetitive blows to the head, potentially leading to a progressive brain disease with later life behavior, mood, and cognitive changes, as well as the development of dementia. We must learn as much as possible, as quickly as possible, in order to determine who may be at increased risk for CTE and other long-term consequences of the repetitive head impacts experienced by athletes at all ages, and to develop methods of preventing and treating the symptoms of CTE. I want to close by thanking the Committee for your interest in addressing this important issue and for your commitment toward improving the health and well-being of older Americans.

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EXHIBIT 14

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FRONTLINE Sports Concussion Watch

76 of 79 Deceased NFL Players Found to Have Brain Disease



As the NFL nears an end to its long-running legal battle over concussions, new data from the nation's largest brain bank focused on traumatic brain injury has found evidence of a degenerative brain disease in 76 of the 79 former players it's examined.

The findings represent a more than twofold increase in the number of cases of chronic traumatic encephalopathy, or CTE, that have been reported by the Department of Veterans Affairs' brain repository in Bedford, Mass.

League of Denial, FRONTLINE's investigation into the NFL's concussion crisis airs tonight on many PBS stations. (Check local listings.)

Researchers there have now examined the brain tissue of 128 football players who, before their deaths, played the game professionally, semiprofessionally, in college or in high school. Of that sample, 101 players, or just under 80 percent, tested positive for CTE.

To be sure, players represented in the data represent a skewed population. CTE can only be definitively identified posthumously, and many of the players who have donated their brains for research suspected that they may have had the disease while still alive. For example, former Chicago Bears star Dave Duerson committed suicide in 2011 by shooting himself in the chest, reportedly to preserve his brain for examination.

Nonetheless, Dr. Ann McKee, the director of the brain bank, believes the findings suggest a clear link between football and traumatic brain injury.

McKee, a neuropathologist who directs the brain bank as part of a collaboration between the VA and Boston University's CTE Center. But "playing football, and the higher the level you play football and the longer you play football, the higher your risk."

An NFL spokesman did not respond to several requests for comment.

CTE occurs when repetitive head trauma begins to produce abnormal proteins in the brain known as "tau." The tau proteins work to essentially form tangles around the brain's blood vessels, interrupting normal functioning and eventually killing nerve cells themselves. Patients with less advanced forms of the disease can suffer from mood disorders, such as depression and bouts of rage, while those with more severe cases can experience confusion, memory loss and advanced dementia.

Among the NFL legends found to have had CTE are Duerson, Hall of Fame Pittsburgh Steelers center Mike Webster and former San Diego Chargers legend Junior Seau. On Monday, ESPN's *Outside the Lines* reported that a New York neuropathologist had discovered signs of CTE in the brain of Jovan Belcher. In 2012, the former Kansas City Chiefs linebacker shot and killed his girlfriend before driving to a Chiefs practice facility, where he committed suicide in front of team officials.

The new data from the VA/BU repository — once the "preferred" brain bank of the NFL — comes as thousands of NFL retirees and their beneficiaries approach an Oct. 14 deadline to decide whether to opt out of a proposed settlement in the class-action concussion case brought against the league by more than 4,500 former players.

The research helps address what had been a key sticking point in negotiations — the issue of prevalence. Players in the lawsuit have accused the league of concealing a link between football and brain disease. While the settlement includes no admission of wrongdoing, actuarial data filed in federal court this month showed the NFL expects nearly a third of all retired players to develop a long-term cognitive problem, such as Alzheimer's disease or dementia, as a result of football.

Under the proposed settlement, the survivors of players found to have died with CTE can qualify for a payment as high as \$4 million. But some, including the family of Junior Seau, have announced plans to opt out of the settlement. Like Duerson, Seau committed suicide in 2012 by shooting himself in the chest with a .357 Magnum revolver. His family has filed a wrongful death suit against the league, arguing in part that the deal does not include adequate compensation for the descendants of former players. An attorney for the family told ESPN this month that the family was not suing "for his pain and suffering. They're suing for their own:"

Others have challenged the settlement's award structure for CTE specifically, claiming it only allows for such payments if a player was diagnosed with the disease before the day that the agreement won preliminary approval in July. This detail, they say, would shut out any player who may be diagnosed in the future.

Brad Karp, an outside counsel for the league, told FRONTLINE in an e-mail that "criticism of the settlement on this ground reflects a profound misunderstanding" of the proposed agreement. "The settlement provides very substantial monetary compensation for players who suffer from the significant neurocognitive symptoms alleged to be associated with CTE and who demonstrate, through diagnostic testing, that they have moderate or severe dementia."

It remains unclear just how many players will decide to either opt out of the settlement, or choose to file a formal objection. A key test will come in November when the judge in the case holds a Fairness Hearing to consider any such challenges. Final approval would not come until sometime soon thereafter.

EXHIBIT 15

The New York Times

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January 18, 2007

Expert Ties Ex-Player's Suicide to Brain Damage

By ALAN SCHWARZ

Since the former National Football League player Andre Waters killed himself in November, an explanation for his <u>suicide</u> has remained a mystery. But after examining remains of Mr. Waters's brain, a neuropathologist in Pittsburgh is claiming that Mr. Waters had sustained brain damage from playing football and he says that led to his <u>depression</u> and ultimate death.

The neuropathologist, Dr. Bennet Omalu of the <u>University of Pittsburgh</u>, a leading expert in forensic pathology, determined that Mr. Waters's brain tissue had degenerated into that of an 85-year-old man with similar characteristics as those of early-stage <u>Alzheimer's</u> victims. Dr. Omalu said he believed that the damage was either caused or drastically expedited by successive concussions Mr. Waters, 44, had sustained playing football.

In a telephone interview, Dr. Omalu said that brain trauma "is the significant contributory factor" to Mr. Waters's brain damage, "no matter how you look at it, distort it, bend it. It's the significant forensic factor given the global scenario."

He added that although he planned further investigation, the depression that family members recalled Mr. Waters exhibiting in his final years was almost certainly exacerbated, if not caused, by the state of his brain — and that if he had lived, within 10 or 15 years "Andre Waters would have been fully incapacitated."

Dr. Omalu's claims of Mr. Waters's brain deterioration — which have not been corroborated or reviewed — add to the mounting scientific debate over whether victims of multiple concussions, and specifically longtime N.F.L. players who may or may not know their full history of brain trauma, are at heightened risk of depression, dementia and suicide as early as midlife.

The N.F.L. declined to comment on Mr. Waters's case specifically. A member of the league's mild traumatic brain injury committee, Dr. Andrew Tucker, said that the N.F.L. was beginning a study of retired players later this year to examine the more general issue of football concussions and subsequent depression.

"The picture is not really complete until we have the opportunity to look at the same group of people over time," said Dr. Tucker, also team physician of the <u>Baltimore Ravens</u>.

The Waters discovery began solely on the hunch of Chris Nowinski, a former <u>Harvard</u> football player and professional wrestler whose repeated concussions ended his career, left him with severe <u>migraines</u> and depression, and compelled him to expose the effects of contact-sport brain trauma. After hearing of the suicide, Mr. Nowinski phoned Mr. Waters's sister Sandra Pinkney with a ghoulish request: to borrow the remains of her brother's brain.

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The condition that Mr. Nowinski suspected might be found in Mr. Waters's brain cannot be revealed by a scan of a living person; brain tissue must be examined under a microscope. "You don't usually get brains to examine of 44-year-old ex-football players who likely had depression and who have committed suicide," Mr. Nowinski said. "It's extremely rare."

As Ms. Pinkney listened to Mr. Nowinski explain his rationale, she realized that the request was less creepy than credible. Her family wondered why Mr. Waters, a hard-hitting N.F.L. safety from 1984 to 1995 known as a generally gregarious and giving man, spiraled down to the point of killing himself.

Ms. Pinkney signed the release forms in mid-December, allowing Mr. Nowinski to have four pieces of Mr. Waters's brain shipped overnight in formaldehyde from the Hillsborough County, Fla., medical examiner's office to Dr. Omalu in Pittsburgh for examination.

He chose Dr. Omalu both for his expertise in the field of neuropathology and for his rare experience in the football industry. Because he was coincidentally situated in Pittsburgh, he had examined the brains of two former <u>Pittsburgh Steelers</u> players who were discovered to have had postconcussive brain dysfunction: Mike Webster, who became homeless and cognitively impaired before dying of heart failure in 2002; and Terry Long, who committed suicide in 2005.

Mr. Nowinski, a former World Wrestling Entertainment star working in Boston as a pharmaceutical consultant, and the Waters family have spent the last six weeks becoming unlikely friends and allies. Each wants to sound an alarm to athletes and their families that repeated concussions can, some 20 years after the fact, have devastating consequences if left unrecognized and untreated — a stance already taken in some scientific journals.

"The young kids need to understand; the parents need to be taught," said Kwana Pittman, 31, Mr. Waters's niece and an administrator at the water company near her home in Pahokee, Fla. "I just want there to be more teaching and for them to take the proper steps as far as treating them.

"Don't send them back out on these fields. They boost it up in their heads that, you know, 'You tough, you tough.' "

Mr. Nowinski was one of those tough kids. As an all-<u>Ivy League</u> defensive tackle at Harvard in the late 1990s, he sustained two concussions, though like many athletes he did not report them to his coaches because he neither understood their severity nor wanted to appear weak. As a professional wrestler he sustained four more, forcing him to retire in 2004. After he developed severe migraines and depression, he wanted to learn more about concussions and their effects.

That research resulted in a book published last year, "Head Games: Football's Concussion Crisis," in which he detailed both public misunderstanding of concussions as well as what he called "the N.F.L.'s tobacco-industry-like refusal to acknowledge the depths of the problem."

Football's machismo has long euphemized concussions as bell-ringers or dings, but what also alarmed Mr. Nowinski, 28, was that studies conducted by the N.F.L. on the effects of concussions in players "went against just about every study on sports concussions published in the last 20 years."

Studies of more than 2,500 former N.F.L. players by the Center for the Study of Retired Athletes, based at the <u>University of North Carolina</u>, found that cognitive impairment, Alzheimer's-like symptoms and depression rose proportionately with the number of concussions they had sustained. That information, combined with the revelations that Mr. Webster and Mr. Long suffered from mental impairment before their deaths, compelled Mr. Nowinski to promote awareness of brain trauma's latent effects.

Then, while at work on Nov. 20, he read on Sports Illustrated's Web site, <u>si.com</u>, that Mr. Waters had shot himself in the head in his home in Tampa, Fla., early that morning. He read appraisals that Mr. Waters, who retired in 1995 and had spent many years as an assistant coach at several small colleges — including Fort Valley (Ga.) State last fall — had been an outwardly happy person despite his disappointment at not landing a coaching job in the N.F.L.

Remembering Mr. Waters's reputation as one of football's hardest-hitting defensive players while with the <u>Philadelphia Eagles</u>, and knowing what he did about the psychological effects of concussions, Mr. Nowinski searched the Internet for any such history Mr. Waters might have had.

It was striking, Mr. Nowinski said. Asked in 1994 by The Philadelphia Inquirer to count his career concussions, Mr. Waters replied, "I think I lost count at 15." He later added: "I just wouldn't say anything. I'd sniff some smelling salts, then go back in there."

Mr. Nowinski also found a note in the Inquirer in 1991 about how Mr. Waters had been hospitalized after sustaining a concussion in a game against <u>Tampa Bay</u> and experiencing a seizure-like episode on the team plane that was later diagnosed as body cramps; Mr. Waters played the next week.

Because of Dr. Omalu's experience on the Webster and Long cases, Mr. Nowinski wanted him to examine the remaining pieces of Mr. Waters's brain — each about the size of a small plum — for signs of chronic traumatic encephalopathy, the tangled threads of abnormal proteins that have been found to cause cognitive and intellectual dysfunction, including major depression. Mr. Nowinski tracked down the local medical examiner responsible for Mr. Waters's body, Dr. Leszek Chrostowski, who via e-mail initially doubted that concussions and suicide could be related.

Mr. Nowinski forwarded the Center for the Study of Retired Athletes' studies and other materials, and after several weeks of back-and-forth was told that the few remains of Mr. Waters's brain — which because Waters had committed suicide had been preserved for procedural forensic purposes before the burial — would be released only with his family's permission.

Mr. Nowinski said his call to Mr. Waters's mother, Willie Ola Perry, was "the most difficult cold-call I've ever been a part of."

When Mr. Waters's sister Tracy Lane returned Mr. Nowinski's message, he told her, "I think there's an outside chance that there might be more to the story."

"I explained who I was, what I've been doing, and told her about Terry Long — and said there's a long shot that this is a similar case," Mr. Nowinski said.

Ms. Lane and another sister, Sandra Pinkney, researched Mr. Nowinski's background, his expertise and

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"I said, 'You know what, the only reason I'm doing this is because you were a victim,' " said Ms. Pittman, Mr. Waters's niece. "I feel like when people have been through things that similar or same as another person, they can relate and their heart is in it more. Because they can feel what this other person is going through."

Three weeks later, on Jan. 4, Dr. Omalu's tests revealed that Mr. Waters's brain resembled that of an octogenarian Alzheimer's patient. Nowinski said he felt a dual rush — of sadness and success.

"Certainly a very large part of me was saddened," he said. "I can only imagine with that much physical damage in your brain, what that must have felt like for him." Then again, Mr. Nowinski does have an inkling.

"I have maybe a small window of understanding that other people don't, just because I have certain bad days that when I know my brain doesn't work as well as it does on other days — and I can tell," he said. "But I know and I understand, and that helps me deal with it because I know it'll probably be fine tomorrow. I don't know what I would do if I didn't know."

When informed of the Waters findings, Dr. Julian Bailes, medical director for the Center for the Study of Retired Athletes and the chairman of the department of neurosurgery at <u>West Virginia University</u>, said, "Unfortunately, I'm not shocked."

In a survey of more than 2,500 former players, the Center for the Study of Retired Athletes found that those who had sustained three or more concussions were three times more likely to experience "significant memory problems" and five times more likely to develop earlier onset of Alzheimer's disease. A new study, to be published later this year, finds a similar relationship between sustaining three or more concussions and clinical depression.

Dr. Bailes and other experts have claimed the N.F.L. has minimized the risks of brain trauma at all levels of football by allowing players who sustain a concussion in games — like <u>Jets</u> wide receiver <u>Laveranues Coles</u> last month — to return to play the same day if they appear to have recovered. The N.F.L.'s mild traumatic brain injury committee has published several papers in the journal Neurosurgery defending that practice and unveiling its research that players from 1996 through 2001 who sustained three or more concussions "did not demonstrate evidence of neurocognitive decline."

A primary criticism of these papers has been that the N.F.L. studied only active players, not retirees who had reached middle age. Dr. Mark Lovell, another member of the league's committee, responded that a study using long-term testing and monitoring of the same players from relative youth to adulthood was necessary to properly assess the issue.

"We want to apply scientific rigor to this issue to make sure that we're really getting at the underlying cause of what's happening," Dr. Lovell said. "You cannot tell that from a survey."

Dr. Kevin Guskiewicz is the director of the Center for the Study of Retired Athletes and a member of U.N.C.'s department of exercise and sport science. He defended his organization's research: "I think that

10/1/2014 Casea18-2012mdDocument Obst 1381658001 Fagee 155 No Date Filed: 108/09/2019 some of the folks within the N.F.L. have chosen to ignore some of these earlier findings, and I question how many more, be it a large study like ours, or single-case studies like Terry Long, Mike Webster, whomever it may be, it will take for them to wake up."

The N.F.L. players' association, which helps finance the Center for the Study of Retired Athletes, did not return a phone call seeking comment on the Waters findings. But Merril Hoge, a former Pittsburgh Steelers running back and current ESPN analyst whose career was ended by severe concussions, said that all players — from retirees to active players to those in youth leagues — need better education about the risks of brain trauma.

"We understand, as players, the ramifications and dangers of paralysis for one reason — we see a person in a wheelchair and can identify with that visually," said Mr. Hoge, 41, who played on the Steelers with Mr. Webster and Mr. Long. "When somebody has had brain trauma to a level that they do not function normally, we don't see that. We don't witness a person walking around lost or drooling or confused, because they can't be out in society."

Clearly, not all players with long concussion histories have met gruesome ends — the star quarterbacks Steve Young and Troy Aikman, for example, were forced to retire early after successive brain trauma and have not publicly acknowledged any problems. But the experiences of Mr. Hoge, Al Toon (the former Jets receiver who considered suicide after repeated concussions) and the unnamed retired players interviewed by the Center for the Study of Retired Athletes suggest that others have not sidestepped a collision with football's less glorified legacy.

"We always had the question of why — why did my uncle do this?" said Ms. Pittman, Mr. Waters's niece. "Chris told me to trust him with all these tests on the brain, that we could find out more and help other people. And he kept his word."

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EXHIBIT 16

Brain and nervous system disorders among

NFL Players

This summary reports findings from a study of brain and nervous system disorders among National Football League (NFL) players. Specifically, we looked at Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease. These disorders affect nerve function, resulting in loss of movement or memory.

The information in this summary is related to your health. You are being sent this because you played for the NFL for at least five seasons during 1959 to 1988.

Study background:

Over 15 years ago, we did a study that found "nervous system" deaths were increased among NFL players. Since then other studies have noted similar concerns.

More recently, studies have identified a condition called chronic traumatic encephalopathy (CTE). CTE has symptoms similar to Alzheimer's, ALS, and Parkinson's. It occurs in people who've had multiple concussions.

Concerns for CTE and other diseases that damage nerve cells are increasing among football players. Because of this, we looked more closely at these kinds of disorders to see if they were higher among NFL players.

The disorders we looked at included:

- Alzheimer's, which is the most common type of dementia. Over time, it can cause memory loss and impacts thinking and talking.
- Parkinson's, which affects movement. It can cause shaking, stiffness, or slow movement of muscles. This can affect facial expressions, talking, walking, and hand movement.
- ALS, also known as Lou Gehrig's disease, which causes weakening of the muscles needed to move, speak, eat, and breathe.



Who was in the study:

We included all who played at least five seasons for the NFL during 1959 to 1988. These 3,439 men were identified using the NFL pension fund. To do this study, we used information from the pension fund database, commercial publications, and death certificates. No surveys or blood samples were taken.

As of 2007, 90% of the 3,439 men in our study were alive; most are now 55 or older. In a study we finished earlier this year, we found the NFL players in our study are living longer than other men in the U.S., on average.

In this study, we found:

- In general, brain and nervous system disorders were more than 3 times higher among players; 17 players died with Alzheimer's, ALS, or Parkinson's compared to 5 men in the U.S. (see graph).
- More speed position players died from these disorders compared to the nonspeed position players.

Speed positions included:

- quarterback
- running back
- halfback
- fullback
- wide receiver

- tight end
- defensive back
- safety
- linebacker

Non-speed positions included:

- defensive linemen
- offensive linemen

Punters/kickers were not included in this analysis.

Looking at the specific brain and nervous system disorders, we found:

- ALS was 4 times higher among players; 7 players died with ALS compared to fewer than 2 men in the U.S.
- Alzheimer's was 4 times higher among players; 7 players died with Alzheimer's compared to fewer than 2 men in the U.S.
- Parkinson's was not increased among players compared to men in the U.S.

Disease	NFL Players	Similar group of men from the US population	Risk?	What does this mean?
ALS	7 out of 3,439 players	less than 2 out of 3,439 people	Risk of dying with ALS was 4 times higher among players	Players are more at risk of ALS
Alzheimer's Disease	7 out of 3,439 players	less than 2 out of 3,439 people	Risk of dying with Alzheimer's was 4 times higher among players	Players are more at risk of Alzheimer's
Parkinson's Disease	3 out of 3,439 players	less than 2 out of 3,439 people	The risk of Parkin- son's was about the same as other U.S. men	The risk of Parkinson's is similar to that of other men
Total	17 out of 3,439 players	5 out of 3,439 people	Risk of dying with a brain or nervous system disorder was more than 3 times higher among players	In general, players are more at risk of disorders that result in loss of movement or memory

Graph: The NFL players in our study may more likely have a disorder that causes loss of memory or movement compared to other men in the U.S.

What this means:

We did this study because:

- 1) A study we did years ago showed nervous system diseases may be higher among NFL players.
- 2) Other studies indicated concern for disorders that result in loss of movement or memory among football players.

We found these kinds of disorders were higher among those in our study. This does not mean that you will get one of these disorders; rather, it suggests that as a former football player, you may have a higher risk compared to someone from the general population. Some studies have found these disorders occur more often among individuals who have had multiple concussions though we were not able to assess this.

What you should do:

We sent you this information because we want you to share it with your doctor.

We recommend you send your doctor a copy of this fact sheet to keep in your file or bring a copy to your next appointment. By letting your doctor know we found some health concerns, your doctor can better monitor you for any early signs, recommend tests, and explore treatment options as soon as possible.

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The NFL has several neurological health-related programs that may benefit players:

- The NFL Neurological Care Program helps players coordinate testing and treatment for neurological-related illnesses. Evaluation and treatment costs are paid for by you or your insurance provider, however if you are eligible and cannot afford evaluation or treatment, you may apply to the NFL Player Care Foundation for a grant to help with costs. Though there are many places you can go for neurological care, there are only six medical centers nationwide that participate in this program. Players interested in the program should contact:
 - 1. Dr. Sam Gandy/Dr. Silvana Riggio (212) 774-1722, Mt. Sinai Medical Center, New York
 - 2. Chris Thrasher (404) 756-8800, Morehouse School of Medicine, Atlanta
 - 3. Dr. David Brody (314) 362-1381, Washington University School of Medicine/Barnes-Jewish Hospital, St. Louis
 - 4. Dr. Mitchel Berger (415) 353-3933, University of California, San Francisco School of Medicine, San Francisco
 - 5. Jesse Fischer (310) 794-7688, University of California, Los Angeles
 - 6. Dr. Gregory Stewart, (504) 864-2104, Tulane University, New Orleans

To learn more about the program and how to participate, visit: www.nfplayercare.com/PlayerCarePlanNeurologicalCare.aspx

- The NFL 88 Plan is a benefit for players suffering from dementia, ALS or Parkinson's disease. The 88 Plan reimburses or pays claims directly to qualified, former players. To learn more about the NFL 88 plan, visit: www.nflplayercare.com/88PlanOverview.aspx
- The Neurocognitive Disability Benefit is new and will soon be available to former players who are eligible and have a permanent neuro-cognitive impairment. The NFL plans to send information on the Neuro-cognitive Disability Benefit to former players.

Learn More:

Alzheimer's Association: www.alz.org/

he Alzheimer's Association website provides information about the differences between normal symptoms of aging compared to progressive memory loss.

ALS Association: www.alsa.org/about-als/

The ALS Association website offers information about symptoms, treatment options, and support groups. Generally, ALS affects about 5 out of every 100,000 people worldwide.

National Parkinson's Foundation (NPF): www.parkinson.org/
The NPF website offers information on symptoms, other illnesses that can mimic Parkinson's, treatment, and how jogyell with Parkinson's.







EXHIBIT 17

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mTBI SPECIAL ISSUE

Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma

Christine M. Baugh • Julie M. Stamm • David O. Riley • Brandon E. Gavett • Martha E. Shenton • Alexander Lin • Christopher J. Nowinski • Robert C. Cantu • Ann C. McKee • Robert A. Stern

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Abstract Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease thought to be caused, at least in part, by repetitive brain trauma, including concussive and subconcussive injuries. It is thought to result in executive dysfunction, memory impairment, depression and suicidality, apathy, poor impulse control, and eventually dementia. Beyond repetitive brain trauma, the risk factors for CTE remain unknown. CTE is neuropathologically characterized by aggregation and accumulation of hyperphosphorylated tau and TDP-43. Recent postmortem findings indicate that CTE may affect a broader population than was initially

conceptualized, particularly contact sport athletes and those with a history of military combat. Given the large population that could potentially be affected, CTE may represent an important issue in public health. Although there has been greater public awareness brought to the condition in recent years, there are still many research questions that remain. Thus far, CTE can only be diagnosed post-mortem. Current research efforts are focused on the creation of clinical diagnostic criteria, finding objective biomarkers for CTE, and understanding the additional risk factors and underlying mechanism that causes the disease. This review examines

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research to date and suggests future directions worthy of exploration.

Keywords Chronic traumatic encephalopathy · Traumatic brain injury · Dementia · Concussion · Tauopathy · Dementia pugilistica

Abbreviations

Aβ Beta amyloid AD Alzheimer's disease

ALS Amyotrophic lateral sclerosis

APOE Apolipoprotein E

APP Amyloid precursor protein
BOLD Blood oxygen level dependent

Cho Choline

CSF Cerebrospinal fluid

CTE Chronic traumatic encephalopathy
CTEM Chronic traumatic enceohalomyelopathy

DTI Diffusion tensor imaging ERP Event-related potential

fMRI Functional magnetic resonance imaging

FDDNP 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-

naphthyl}ethylidene)malononitrile

FTD Frontotemporal dementia

GT Glial tangle GRN Granulin

MAPT Microtubule-associated protein tau MRI Magnetic resonance imaging MRS Magnetic Resonance Spectroscopy

NAA N-acetyl asparate
NFT Neurofibrilary tangle
NT Neurophil thread

PCS Post-concussion syndrome PET Positron emission tomography

SPECT Single photon emission computed tomography

SWI Susceptibility weighted imaging TDP-43 TAR DNA-binding protein 43

TBI Traumatic brain injury

Introduction

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease thought to be caused, at least in part, by repetitive brain trauma that can occur during contact sports and military participation (McKee et al. 2009). This trauma can include mild traumatic brain injury (mTBI), or concussions, as well as subconcussive injuries, that is, mild brain trauma that does not result in the readily observable signs and symptoms of a concussion (Gavett et al. 2011a; McKee et al. 2009; Spiotta et al. 2011; Stern et al. 2011a). CTE is distinct from the acute sequelae of concussion or traumatic

brain injury (TBI), and is not merely prolonged post-concussive syndrome (PCS) (Gavett et al. 2011b). While post-concussive syndrome symptoms endure following an acute concussion without complete relief of symptoms of the initial injury, the symptoms of CTE typically do not present until years after the trauma-producing activity, and the symptoms of initial injury, if any, have ended. CTE is pathologically distinct from other neurodegenerative diseases, including Alzheimer's disease and Frontotemporal Lobar Degeneration (Corsellis et al. 1973; McKee et al. 2009).

For almost a century, it has been known that repeated blows to the head are associated with cognitive and behavioral impairments later in life. One of the first publications on the topic was a 1928 paper by Martland who called the condition he observed in boxers, "punch drunk." Martland hypothesized that the symptoms he observed resulted from the repeated blows to the head that these fighters took during their careers (1928). In 1937, Millspaugh outlined the disease marked by motor deficits and cognitive dysfunction under the name "dementia pugilistica," as he too observed the disorder primarily in boxers. Corsellis and colleagues presented a 15 case series in 1973 that neuropathologically distinguished dementia pugilistica from other neurodegenerative disorders.

Although the term Chronic Traumatic Encephalopathy (CTE) was first used in the literature in the 1960's, the disease's ability to affect a broader population beyond boxers was not fully recognized until more recently (McKee et al. 2009; Omalu et al. 2005; Omalu et al. 2006). Since that time, CTE has been found in others with a history of repetitive concussions from sports (e.g., American football players, professional wrestlers, professional hockey players) and from other activities (e.g., a victim of physical abuse, an epileptic, a self-injurer, a circus clown who was repeatedly shot out of a cannon) (Gavett et al. 2011b; Geddes et al. 1999; Hof et al. 1991; McKee et al. 2009; Omalu et al. 2005; Omalu et al. 2006; Omalu et al. 2010; Roberts et al. 1990; Stern et al. 2011a). Also, in recent years, our group at the Boston University Center for the Study of Traumatic Encephalopathy (CSTE) has found neuropathologically confirmed CTE in football players with no history of diagnosed or reported concussions (but who played positions, such as lineman, with the greatest exposure to repetitive hits to the head [Greenwald et al. 2008]), suggesting that repetitive subconcussive trauma, not just symptomatic concussions, may also lead to the development of this neurodegenerative disease (Gavett et al. 2011a; McKee et al. 2009). This paper will review research on CTE to date including its risk factors, clinical presentation, and neuropathology. In addition it will explore future directions for CTE research with a specific focus on methods that may be useful for in vivo diagnosis, including neuroimaging techniques.

Clinical presentation and course

To date, more than 70 retrospective clinical examinations have been conducted by the CSTE with the family members of deceased athletes and military personnel whose brains have been donated for study. The information obtained from the semistructured interview is combined with a review of patient medical records and analyzed by the neuropsychologist [RAS] to gain an understanding of the clinical presentation and progression of the deceased brain donors whose ages range from teens to 80s. During this process the neuropsychologist remains blind to the neuropathological diagnosis, helping to eliminate potential bias; similarly, the neuropathologist [ACM] remains blind to the clinical history and medical records until the neuropathological examination and diagnosis is complete. From these interviews we have been able to gain a greater understanding of the clinical presentation and course of CTE. Although a clinical "picture" of CTE has been created using these retrospective measures, there are currently no consensus-based or prospective neuropathologically validated clinical diagnostic criteria.

Neuropsychological and neuropsychiatric changes

The cognitive and behavioral symptoms associated with CTE are reflective of the regions that have been pathologically determined to be most affected by CTE. As will be explained in further detail in the neuropathology section of this paper, the regions of the brain most severely damaged by CTE include the cerebral cortex and the medial structures of the limbic system (amygdala, mammillary bodies, hippocampus, etc.) (Gavett et al. 2011a; Stern et al. 2011a). The severity of the clinical manifestation progresses through the course of the disease as the neurodegeneration increases (Stern et al. 2011a).

The neuropsychological and neuropsychiatric changes associated with CTE can be classified into the categories of cognition, mood, and behavior (Table 1). CTE presents with changes in each branch of this symptom triad and the severity of the symptoms appears to progress with the course of the disease. These symptoms generally begin years or decades after repeated brain trauma, when the neurodegeneration is severe enough to manifest clinical symptoms (Stern et al. 2011a). The earliest neuropathological stages of CTE may present without clinical symptoms (Stern et al. 2011a). Early cognitive symptoms primarily include learning and memory impairment as well as executive dysfunction. Mood changes typically include depression, apathy, and irritability, as well as suicidality. The behavioral changes primarily include poor impulse control, with individuals described as having a "short fuse" or being "out of control." Aggression and increased violence are

Table 1 Early symptoms of chronic traumatic encephalopathy

Domain	Symptoms	
Cognitive	Memory Impairment	
	Executive Dysfunction (e.g., problems with planning, organization, multi-tasking, judgment)	
Mood	Depression	
	Apathy	
	Irritability	
	Suicidality	
Behavior	Impulse Control Problems (e.g., "short fuse," "out of control")	
	Disinhibition	
	Substance Abuse and Other Addictions	
	Aggression and Increased Violence	

often experienced. Disinhibition and problems with substance and other forms of abuse also occur. Later in the disease course, these cognitive, mood, and behavioral impairments worsen, with dementia evident in all older cases (i.e., 65 years or greater) with advanced stage CTE.

As with most neurodegenerative causes of dementia, the later in the course a patient with CTE is seen, the more difficult it is to differentiate the specific underlying disease based on clinical presentation. That is, once an adequate amount of neural tissue is destroyed, differential diagnosis of most cases of moderate-severe dementia is difficult just based on current presentation. However, the early presentation and course of CTE can distinguish it from most other causes of dementia. The closest symptom profile to CTE is that caused by FTLD, behavioral variant. The symptoms of FTLD typically begin between the ages of 45-65, there is a somewhat rapid symptom progression, and there is a positive family history in approximately 40 % of cases. In contrast, the early symptoms of CTE (Table 1) typically present between the ages of 30 and 50, there is a slow, prolonged course of progression, and there does not appear to be a familial risk. Although not a completely definitive method of distinguishing between CTE and FTLD behavioral variant, all cases of CTE will have had a history of exposure to repetitive brain trauma, whereas FTLD will not typically have such a history.

It is important to note that although CTE is thought to result from repeated mTBI, it is separate from the acute PCS, and it is not the accumulation of immediate symptoms from multiple concussive or subconcussive events. PCS is not thought to directly cause CTE pathology. Given the noticeable overlap in symptomology between PCS and CTE and the fact that, in some cases, there may be overlap in the onset and expression of the two disorders, differentiating between the two can sometimes be difficult (Stern et al. 2011a).

Clinicopathological associations

In a review of the world's published case studies of neuropathologically confirmed CTE (the vast majority being boxers), McKee et al. noted that 63 % (32 of 51) had memory loss (2009). Like AD, those with CTE appear to have anterograde amnesia, or difficulty remembering newly learned information (Sperling et al. 2010). This is consistent with the deterioration of the hippocampus and other medial temporal structures seen in cases of CTE. Further, individuals with CTE commonly have executive dysfunction (Omalu et al. 2011). Executive functions refer to a group of cognitive abilities responsible for goal-directed behaviors (Stern et al. 2011b); individuals with CTE often have impaired judgment, poor insight, and disinhibition (Gavett et al. 2011a). This symptomology seems to reflect the neuropathologic changes and atrophy of the frontal lobes described by McKee et al. in almost all CTE cases (2009).

Mood and behavior changes are hallmark features of CTE (McKee et al. 2009; Omalu et al. 2011). As with changes from other neurodegenerative diseases, the mood and behavioral changes associated with CTE are often the most concerning to family members and caregivers (Stern et al. 2011b). These clinical manifestations are consistent with the neuropathologic changes in the medial temporal lobe (especially the amygdala) and orbitofrontal regions. The combination of altered emotional responses (including rage) from amygdala involvement and disinhibition and reduced impulse control from frontal involvement appears to lead to many of the more significant clinical manifestations of the disease, including suicidality (Gavett et al. 2011b).

Neurological and motor changes

CTE often results in neurologic dysfunction, especially alterations in movement and motor coordination. These signs include difficulty with balance and gait (parkinsonism) and speech changes (including slowed, slurred, and dysarthric speech) (McKee et al. 2009). In a smaller portion of cases, there appears to be abnormalities in gaze (McKee et al. 2009). A small subset of individuals with CTE have a variant referred to as chronic traumatic encephalomyelopathy (CTEM) that also affects the spinal cord and is associated with motor neuron disease, clinically mimicking Amyotrophic Lateral Sclerosis (ALS), or Lou Gehrig's disease (McKee et al. 2010). These individuals have a different and more severe neurologic profile including clinical evidence of motor neuron disease as marked by progressive muscle weakness and atrophy, fasciculations, balance and gait problems, dysphagia, and hyperactive deep tendon reflexes (McKee et al. 2010).

Neuropathological characteristics

Neuropathological findings of CTE were first described by Corsellis et al. (1973). McKee and colleagues at the CSTE reviewed the world's literature of neuropathologically confirmed CTE and found 49 cases at the time (2009). These 49 cases, along with three new cases from the CSTE were described in 2009 by McKee et al. Since that time, the VA CSTE Brain Bank has grown from the original three to over 100 brains with over 60 cases of neuropathologically diagnosed CTE thus far (i.e., not all of the remaining 40 brains have had completed examinations to date), making it, by far, the largest CTE tissue repository in the world. The gross and microscopic neuropathology of CTE described below is based on the combination of the previous literature review and the findings from the VA CSTE Brain Bank.

Gross pathological characteristics

Advanced stages of CTE are accompanied by generalized atrophy of the brain with reduced brain weight, as well as atrophy of the frontal and temporal cortices and medial temporal lobe (McKee et al. 2009). There is often pronounced atrophy of the thalamus, hypothalamus, and mammillary bodies. Thinning of the corpus callosum and generalized atrophy of the cerebral subcortical white matter is common. Pallor of the substantia nigra and locus coeruleus is also a typical feature of advanced CTE. Dilation of the lateral and third ventricles, anterior cavum septum pellucidum, and posterior septal fenestrations are frequent findings (McKee et al. 2009).

A cavum septum pellucidum occurs when the leaflets of the septum pellucidum are separated and the space is filled with cerebrospinal fluid (Tubbs et al. 2011). Repetitive concussive and subconcussive brain trauma likely produces a fluid wave within the ventricles that damages the septum pellucidum (Gavett et al. 2011a; McKee et al. 2009). Cavum septum pellucidum was found in 12 of 13 boxers studied by Corsellis et al. (1973).

Microscopic neuropathological characteristics

Microscopically, CTE is characterized by accumulation of phosphorylated tau protein as neurofibrillary tangles (NFTs), neurites, and glial tangles (GTs) throughout the frontal, insular, and temporal cortices; diencephalon; brainstem; cerebellar dentate nucleus and spinal cord. Figure 1 demonstrates phosphorylated tau deposition in CTE brains as compared to normal control. Accumulations of TAR DNA-Binding Protein 43 (TDP-43) as neuronal and glial inclusions, neurites and intranuclear inclusions are also found in CTE and are usually most prominent in cases with severe tau pathology. Prominent neuronal loss is seen in the

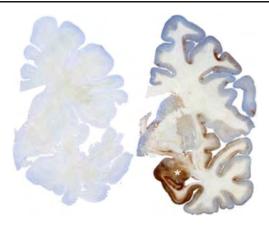


Fig. 1 Neuropathological analysis section. Coronal sections of a brain immunostained for hyperphosphorylated tau protein and counterstained with cresyl violet. The normal brain on the left shows no deposits of hyperphosphorylated tau protein. The brain on the right with CTE shows irregular tau deposits (*dark brown* discoloration) in the cerebral cortex. There are also dense tau NFTs in the amygdala (*asterisk*), entorhinal cortex and medial temporal lobe

hippocampus, entorhinal cortex, and amygdala as well as less severe degrees of neuronal loss in the subcallosal and insular cortex, olfactory bulbs, mammillary bodies, locus coeruleus, substantia nigra, medial thalamus and cerebral cortex (McKee et al. 2009).

The tau-immunoreactive neurofibrillary pathology is characteristically irregular and affects primarily the superficial cortical layers with focal epicenters at the depths of the sulci and surrounding small blood vessels. Tau-immunoreactive NFTs may be particularly dense in the hippocampus, amygdala, entorhinal cortex and olfactory bulbs in advanced stages of the disease (Gavett et al. 2011a; McKee et al. 2009).

Although the specific tau isoforms found in CTE are indistinguishable from AD (Schmidt et al. 2001), the irregular nature of tau deposition and the perivascular clustering of tau-immunoreactive abnormalities at the depth of the sulci are unique to CTE and distinguish it from other tauopathies, including AD (McKee et al. 2009). In addition, the density of the NFTs and GTs is often far greater in CTE than in other tauopathies (Gavett et al. 2011a).

TDP-43 immunoreactivity is most commonly seen in the frontal and medial temporal cortices, brainstem, diencephalon, insula, subcortical white matter, substantia nigra pars compacta, amygdala, hippocampus, caudate, putamen, thalamus, and hypothalamus (McKee et al. 2010; Stern et al. 2011a). TDP-43 immunoreactive inclusions have been found throughout the anterior horn of the spinal cord and motor cortex in a subset of individuals with CTEM (McKee et al. 2010; Stern et al. 2011a).

 $A\beta$ deposition is an inconsistent finding in CTE. While neuritic $A\beta$ plaques are an essential feature of AD, A β is found in only 40–45 % of CTE cases (McKee et al. 2009). When $A\beta$ is present in CTE, it generally consists of

primarily diffuse plaques with relatively few neuritic plaques (McKee et al. 2009). The presence of tau proteinopathy has been shown to enhance $A\beta$ neurotoxicity (Mann et al. 1990; Roberson et al. 2007).

Brain trauma and other risk factors

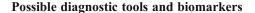
To date, all pathologically diagnosed cases of CTE have come from individuals with a history of repetitive brain trauma (McKee et al. 2009). As such, it seems that repetitive trauma is necessary for incurring CTE; however, there are numerous individuals with a history of repeated brain trauma who do not have CTE upon neuropathological examination. Therefore, concussions and other brain trauma alone are not sufficient to cause the disease. Importantly, it is also possible that this repetitive trauma does not necessarily have to be at the concussive (mTBI) or more structural (e.g., TBI) level (Gavett et al. 2011b; McKee et al. 2009; Stern et al. 2011a). Subconcussive brain injury (Spiotta et al. 2011), or a blow to the head with adequate g force to produce a non-structural brain injury (though with the neuronal changes of concussion) that does not result in apparent clinical symptoms, may be a sufficient trauma load to initiate the neurodegenerative cascade (Gavett et al. 2011b; McKee et al. 2009; Stern et al. 2011a). Given that repetitive brain trauma is necessary, but not sufficient, it is evident that other risk factors may be involved in initiating or mediating CTE.

Although all individuals with neuropathologically confirmed CTE have had repetitive brain trauma, the nature of this trauma is a crucial factor that requires further scientific investigation. The age at which the brain starts being exposed to trauma may be a critical factor in determining whether or not an individual develops CTE. It is possible that assaulting a young brain, which is still developing and more vulnerable to injury, may have more catastrophic consequences later in life (Schneider 1979). This theory has yet to be validated, but it has been shown that concussions and brain injuries in youth result in more severe and longer lasting cognitive deficits (Field et al. 2003; Pullela et al. 2006). Additionally, it is not understood whether or not the severity and frequency of the brain trauma influence the development of CTE. Within a given sport, position could play a significant role. A recent study utilizing accelerometers placed inside the helmets of college football players found that there were significant differences in the exposure to brain trauma based on position (Crisco et al. 2010). Further, a study by Talavage and colleagues examined a cohort of high school football players and showed measurable neurocognitive and neurophysiologic

deficits after hits to the head that did not cause any reported symptoms of concussion (2010). Importantly, individuals who received subconcussive blows were unlikely to undergo clinical assessment and thus continued playing in the game, exposing their brains to further injury (Talavage et al. 2010).

Some individuals may have a genetic predisposition to developing CTE. Initial studies indicate that the apolipoprotein E (APOE) gene's ε4 allele may be a useful area of investigation. APOE is the strongest susceptibility gene for Alzheimer's disease (AD). APOE ε4 has also been associated with longer recovery time and more severe cognitive deficits following single TBI in boxers and professional football players (Jordan et al. 1997; Kutner et al. 2000; Teasdale et al. 1997). APOE ε4 carriers have also been shown to have worse outcomes both in the short-term and in the long-term following head injury (Friedman et al. 1999; Jordan et al. 1997; Katzman et al. 1996; Teasdale et al. 1997). In contrast to its role in AD, it is thought that APOE £4 may decrease the capacity to repair damage following brain injury (Crawford et al. 2009). Further, older retired football players who were \$4 carriers were shown to have lower cognitive performance (Kutner et al. 2000). Additionally, in a sample of 12 neuropathologically confirmed cases of CTE, 5 (42 %) cases were ε4 carriers with 2 (17 %) of those cases being ε4 homozygous (McKee et al. 2010). This is in contrast to population prevalence studies of the APOE £4 allele that have shown that at least one £4 allele is carried by 27-29 % of the population and that ε4 homozygosity only occurs in 1–2 % of the population (Hill et al. 2007). Much more research is required to substantiate the possible link between APOE $\varepsilon 4$ and CTE.

There are numerous other risk factors that require further investigation. While it has been shown that females are diagnosed with more concussions and tend to have prolonged recoveries, it is unknown whether this is due to differential symptom reporting between males and females, possibly weaker neck and upper body strength in women, the potential role in sex hormones in concussion, or other variables. It is also unknown whether females have a different CTE-risk profile than their male counterparts (Covassin and Elbin 2011; Dick 2009). To date, the large majority of brains studied with CTE have been male due to the bias of brain donations to date being made by families of deceased football and other collision sport athletes. Furthermore, an individual's "cognitive reserve" or "brain reserve" may affect the timing of the clinical manifestation of CTE. More specifically, given approximately the same level of neurodegeneration, an individual with a greater cognitive or brain reserve may be less likely to display clinical signs and symptoms of CTE than an individual with a lesser reserve (Schneider 1979). This finding has been shown in several studies of AD and other neurodegenerative diseases (Stern 2007).



As with other neurodegenerative diseases, such as AD, FTLD, and Lewy-Body Disease, CTE can only be diagnosed neuropathologically. However, in recent years progress has been made in improving in vivo diagnostic accuracy, especially for AD, through an integration of clinical diagnostic features (e.g., neurological and neuropsychological evaluations, history, course) with more objective biomarkers of disease (Dubois et al. 2007; De Meyer et al. 2010). These biomarker methods include: measurement of proteins through CSF and blood (including beta amyloid and tau), as well as through PET neuroimaging techniques with ligands for beta amyloid; structural neuroimaging (e.g., measurement of hippocampal volume); biochemical neuroimaging (e.g., magnetic resonance spectroscopy; MRS); and genetic susceptibility markers (e.g., APOE genotyping). These approaches have now led to significant changes to research diagnostic criteria for AD, incorporating both clinical and biomarker criteria (Jack et al. 2011; McKhann et al. 2011). A major goal of this new diagnostic approach is to be able to detect disease prior to dementia and even prior to symptom onset in order to intervene more successfully with disease modifying agents when they become available (Sperling et al. 2011).

Similar approaches to accurate in vivo diagnosis of CTE seem quite plausible, utilizing the knowledge already gained in AD biomarker research. In addition to CSF and blood measurements of proteins and genotyping of potential susceptibility genes, there appears to be a large array of neuroimaging techniques that would be appropriate for CTE diagnostic purposes. Of course, as with AD clinical diagnostic criteria, these techniques—if found to be sensitive and specific to CTE—would be part of a multifactorial diagnostic approach, including clinical evaluations and history, as well as CSF and blood measures of proteins. The potential neuroimaging approaches are explored below.

Structural and volumetric magnetic resonance imaging

Gross neuropathological changes attributed to CTE indicate that Magnetic Resonance Imaging (MRI) may be a useful diagnostic technique. Volumetric MRI can detect whole brain atrophy as well as atrophy of specific areas of interest (e.g., amygdala) present in CTE, as well as cavum septum pellucidum with or without fenestrations (McKee et al. 2009). The ability of volumetric MRI to grossly detect CTE-related atrophy was demonstrated in an initial pilot study examining 5 former professional contact sport athletes with CTE-like symptoms (Gavett et al. 2011b).



Susceptibility weighted imaging

A proposed mechanism of CTE pathogenesis begins with a disruption in the blood brain barrier and changes in the cerebral vasculature (Gavett et al. 2011b; McKee et al. 2009). This, along with the hallmark findings of perivascular tau deposition in CTE, indicates that Susceptibility Weighted Imaging (SWI) (a method of detecting microhemorrhages) could be useful for differential diagnosis of CTE. SWI has been found to detect microhemorrhages resulting from neurotrauma (Ashwal et al. 2006). SWI's current predictive validity has been limited in adults, but there has been some success in utilizing SWI to determine long-term outcome following TBI in children (Chastain et al. 2009; Colbert et al. 2010). More research is required to determine SWI's clinical utility for understanding the longterm effects of repeated brain trauma, including CTE, in adults (Gavett et al. 2011b).

Diffusion tensor imaging

Diffusion Tensor Imaging (DTI) is sensitive to diffuse axonal injury (see Shenton et al. for a review of structural neuroimaging findings, including DTI, in mTBI in this issue.). This is thought to be one of the causal mechanisms involved in CTE, but is also known to be an injury indicative of acute and chronic TBI (Liu et al. 1999; Prabhu 2011). DTI has been used in both animals and humans to examine the effects of brain trauma (Immonen et al. 2009; Lipton et al. 2009). However, knowledge of DTI's usefulness in CTE research is limited. In experimental models in rats, DTI has been shown to be predictive of long-term outcomes following TBI (Immonen et al. 2009). DTI has supported the link between executive dysfunction and axonal injuries in humans (Lipton et al. 2009). Further, in our pilot study of 5 former professional athletes, there was an association between overall exposure to repetitive brain trauma and degradation of callosal white matter nerve fiber bundles (Shenton et al. unpublished; Fig. 2). Figure 2 demonstrates the callosal nerve fiber degradation in the contact sport athlete brain as compared to normal control brain.

Functional magnetic resonance imaging

Functional Magnetic Resonance Imaging (fMRI) has been useful in understanding brain-behavior relationships in numerous neurologic diseases (Seeley et al. 2009). Additionally, blood oxygen level dependent (BOLD) fMRI has been able to differentiate between various types of neurodegeneration including AD, FTD, and dementia with Lewy bodies (Galvin et al. 2011; Zhou et al. 2010). Recent studies of high school football players have utilized fMRI and found significant changes (from pre-season to post-season) in fMRI

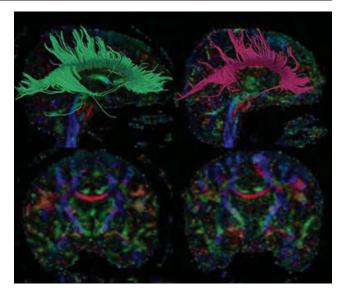


Fig. 2 Diffusion tensor imaging section. Diffusion tensor images captured on a 3 T magnet analyzed with streamline tractography using Slicer 3. Control brain on the left and the brain of a former professional boxer in his 40's on the right. The top two images are sagittal views with the callosal fiber tracts delineated; it is notable that the boxer's fiber tracts are markedly shorter than the control. The bottom two images are a coronal view of the same two individuals and it can be seen that the athlete's corpus callosum (*red* structure in the middle of the brain) is noticeably thinner than the control

results in those athletes with repetitive subconcussive hits (as determined by helmet accelerometer data) (Talavage et al. 2010). Given its current uses, it is possible that fMRI will be helpful in determining brain-behavior associations in CTE as well as differentiating CTE from other neurodegenerative disorders (Gavett et al. 2011b).

Magnetic resonance spectroscopy

Magnetic Resonance Spectroscopy (MRS) utilizes the same clinical MR scanners utilized for MRI to non-invasively measure in vivo brain biochemical metabolites (see Lin et al. for a review of MRS in TBI in this issue). MRS studies have found significant chemical changes in the brains of individuals with various levels of brain trauma; however, most of these studies have been conducted in the acute, rather than the long-term, time frame (Ashwal et al. 2000; Brooks et al. 2001; Cimatti 2006; Henry et al. 2010; Holshouser et al. 2005; Ross et al. 1998; Shutter et al. 2004; Vagnozzi et al. 2008).

However, there has been one pilot study examining the utility of MRS for determining the long-term effects of repetitive brain trauma and possible CTE. In this small-scale study, Lin and colleagues found significant increases in Cho and Glx in former athletes with a history of repetitive brain trauma as compared to age-matched controls (Lin et al. 2010).



Positron emission tomography

Current Positron Emission Tomography (PET) ligands are useful for AD. However these ligands selectively bind to beta-amyloid (e.g., Pittsburgh Compound B or PiB, florbetapir) or bind to both beta-amyloid and tau (2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) malononitrile; FDDNP). However, CTE is primarily a tauopathy with only infrequent beta-amyloid. In cases when it is present, the beta amyloid is aggregated into more diffuse plaques rather than neuritic plaques (McKee et al. 2009). Therefore, tau-selective ligands are likely to play a critical role in in vivo biomarker detection of CTE. Unfortunately, these ligands are not yet available for human imaging.

Single photon emission computed tomography

Single Photon Emission Computed Tomography (SPECT) scans measure regional cerebral blood flow. As such, SPECT is often a sensitive tool for detecting regional abnormalities in brain function. However, the specificity of SPECT is poor (e.g., Masterman et al. 1997). In a recent study comparing a group of retired NFL players and a control group, Amen reported significant differences on SPECT (2011). However, there were many methodological problems with the study, making it difficult to appropriately interpret their results.

Discussion

Although public awareness and media attention surrounding the long-term effects of repetitive concussions and other brain trauma have increased in recent years, scientific knowledge regarding CTE has progressed more slowly, i.e., at a typical speed of scientific discovery. Research related to CTE has been limited thus far, and there are still many questions about this disorder. In fact, some aspects of CTE remain controversial, including the relationship between CTE and other neurodegenerative diseases, such as AD and FTD. Recent research suggests that this disease, previously only known to affect boxers, may be problematic for a much broader population, including other athletes and military personnel. As such, there is an even greater need to understand the mechanism behind this disease (e.g., Blaylock and Maroon 2011), its incidence and prevalence, and how to diagnose, treat, and prevent the disease during life. Knowledge of risk factors could allow for interventions that would help prevent the disease in the future. For example, if an age threshold is found (e.g., individuals who do not experience any brain trauma exposure before a certain age, X, do not go on to develop CTE), then appropriate

recommendations and policy changes could follow, (e.g., limiting or restricting activities with brain trauma exposure in children under the age of X). In addition, it is critical to improve understanding of the severity and number of hits necessary to initiate the neurodegenerative cascade leading to CTE. It may be the case that fewer, more severe TBIs result in a different outcome than more frequent, but less severe concussions or subconcussive blows. The different types of forces incurred by the brain during various activities could prove important; however, further research is necessary.

CTE research should utilize the advances made in research of other neurodegenerative diseases such as AD in order to progress most rapidly. For example, Similarities between CTE and other neurodegenerative diseases provide insight into other genes that may be involved in CTE and are therefore worth investigating. Based on studies of other neurodegenerative diseases, additional genetic factors worthy of consideration may be the TARDBP gene involved with TDP-43 protein production in frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS), the GRN gene involved with the production of granulin and associated with FTLD, and the MAPT gene associated with tau protein and FTLD, as well as other genes associated with causes of dementia and/or motor neuron disease.

Examining the applicability of the neuroimaging modalities outlined in this paper as well as clinical measures, basic translational research, animal modeling, and epidemiologic studies will all help advance knowledge of CTE. Increased scientific knowledge about CTE will assist policy makers (e.g., league officials, legislators, military leadership) in creating appropriate guidelines for prevention and treatment of brain trauma whether in the sports arena or on the military battlefield.

Ongoing and future research

Research related to CTE is in its infancy. Although the neuropathology of CTE has been elucidated in recent years, important areas of research remain, including investigations of CTE's epidemiology, specific risk factors (in addition to repetitive brain trauma exposure), underlying disease mechanism, and the ability to diagnose CTE during life. The development of biomarkers for the purpose of early detection, differential diagnosis, treatment, and prevention has been an important goal of research in other neurodegenerative diseases, such as AD, FTLD, lewy body dementia, and others, and it is also the goal of future CTE research at the BU CSTE (Stern et al. 2011a). With funding from the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, and the National institute of Child Health and Human Development, our group is in



the early stages of research investigating potential biomarkers for CTE. This research will includes a number of the diagnostic tools described above, including volumetric MRI, DTI, SWI, MRS, CSF protein determination, and genetic testing, as well as neuropsychological, psychiatric, and neurological examinations. The goal of this research is to create valid diagnostic criteria though the combination of clinical symptoms, history, and objective biomarkers. This research could lead to the ability to diagnose CTE in the early stages of the disease, possibly before the symptoms of the disease present themselves. Neuroimaging strategies could lead to non-invasive methods of diagnosing CTE in the living. Additionally, genetic testing may indicate specific predisposing factors, such as APOE ε4, that could assist in identifying at-risk individuals. In theory, the earlier we are able to diagnose CTE, the better effect interventions may have on the symptoms and disease progression.

Conclusion

CTE is a progressive neurodegenerative disease linked to repetitive brain trauma from contact sports and other activities. The disease is distinct from post-concussive syndrome or the additive symptomatic effect of multiple concussions. Rather, symptoms begin years or decades after brain trauma exposure and include a triad of cognitive, mood, and

behavioral impairments. Neuropathologically distinct from other neurodegenerative diseases, CTE is characterized by hyperphosphorylated tau and TDP-43 deposition. As with other neurodegenerative diseases, such as AD, CTE can only be diagnosed postmortem at this time. However, unlike AD, CTE research is in its infancy, and there are neither published and validated clinical diagnostic criteria nor biomarkers for the disease. As such, there are many unanswered questions about the development of CTE. Although it is believed that repetitive brain trauma is associated with the neuropathogenesis of the disease (Stern et al. 2011a), whether CTE can occur following a single traumatic brain injury in at-risk individuals is not yet known. The type, number, and severity of concussive and/or subconcussive hits necessary to trigger the neurodegenerative cascade leading to CTE has yet to be determined (Gavett et al. 2010). Moreover, other factors, including duration of exposure to head trauma, age at first exposure, gender, age, race, and genetic predisposition, may play a role in the development of CTE, although further research is needed in these areas (Gavett et al. 2010; McKee et al. 2009; Stern et al. 2011a). Given its potential to impact a broad population of those who have experienced repetitive brain trauma, CTE is an important public health issue. A critical first step is the ability to diagnose CTE during life. Several neuroimaging techniques have the potential to serve as biomarkers for the disease.

Summary

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease thought to be caused, in part, by repetitive concussive and subconcussive brain injury, such as those received in contact sports and military participation.

Although repetitive brain trauma seems necessary for the development of CTE, this alone is not sufficient to cause the disease. Additional risk factors such as longer duration of exposure to head trauma, age at first exposure, and genetic predisposition, may also play a role in the development of CTE, although more research is needed in these areas.

The neuropsychological and neuropsychiatric symptoms associated with CTE fall into three categories: cognition, mood, and behavior. These symptoms, including memory impairment, executive dysfunction, depression, apathy, irritability, suicidality, lack of impulse control, aggression, and disinhibition, tend to worsen with advanced stages of the disease. Later stages of disease are associated with dementia.

Gross neuropathological features of CTE include: atrophy of the frontal and medial temporal lobes, hippocampus, entorhinal cortex, mammillary bodies, and amygdala; dilation of the lateral and third ventricles; anterior cavum septum pellucidum; posterior septal fenestrations, thinning of the corpus callosum and hippocampal floor, and pallor of the substantia nigra. Microscopically the disease is characterized by widespread neuronal loss and gliosis and extensive tau and TDP-43 proteinopathy with a relative absence of beta amyloid deposits.

At this time CTE can only be diagnosed postmortem, as there are no validated clinical diagnostic criteria or biomarkers for the disease. A goal of future research is to establish biomarkers using various neuroimaging tools, such as structural and volumetric MRI, susceptibility weighted imaging, diffusion tensor imaging, magnetic resonance spectroscopy, and positron emission tomography, that can detect the disease in the early stages, possibly prior to symptom onset. This may allow for successful intervention with disease modifying agents once available.

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Conflict of interest No authors on this paper have conflicts of interest to disclose.

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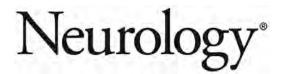
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EXHIBIT 18



Neurodegenerative causes of death among retired National Football League players

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Neurodegenerative causes of death among retired National Football League players

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ABSTRACT

Objective: To analyze neurodegenerative causes of death, specifically Alzheimer disease (AD), Parkinson disease, and amyotrophic lateral sclerosis (ALS), among a cohort of professional football players.

Methods: This was a cohort mortality study of 3,439 National Football League players with at least 5 pension-credited playing seasons from 1959 to 1988. Vital status was ascertained through 2007. For analysis purposes, players were placed into 2 strata based on characteristics of position played: nonspeed players (linemen) and speed players (all other positions except punter/kicker). External comparisons with the US population used standardized mortality ratios (SMRs); internal comparisons between speed and nonspeed player positions used standardized rate ratios (SRRs).

Results: Overall player mortality compared with that of the US population was reduced (SMR 0.53, 95% confidence interval [CI] 0.48-0.59). Neurodegenerative mortality was increased using both underlying cause of death rate files (SMR 2.83, 95% CI 1.36-5.21) and multiple cause of death (MCOD) rate files (SMR 3.26, 95% CI 1.90-5.22). Of the neurodegenerative causes, results were elevated (using MCOD rates) for both ALS (SMR 4.31, 95% CI 1.73-8.87) and AD (SMR 3.86, 95% CI 1.55-7.95). In internal analysis (using MCOD rates), higher neurodegenerative mortality was observed among players in speed positions compared with players in nonspeed positions (SRR 3.29, 95% CI 0.92-11.7).

Conclusions: The neurodegenerative mortality of this cohort is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an increased risk of neurodegenerative disease among football players. **Neurology® 2012;79:1970-1974**

GLOSSARY

AD = Alzheimer disease; ALS = amyotrophic lateral sclerosis; CI = confidence interval; CTE = chronic traumatic encephalopathy; ICD = International Classification of Diseases; MCOD = multiple cause of death; NDI = National Death Index; NFL = National Football League; NIOSH = National Institute for Occupational Safety and Health; PD = Parkinson disease; SMR = standardized mortality ratio; SSR = standardized rate ratio.

In 1994, the National Institute for Occupational Safety and Health (NIOSH) conducted a mortality study of National Football League (NFL) players. One notable result was an increase in "nervous system" deaths due to 4 cases of amyotrophic lateral sclerosis (ALS). Little additional study on neurologic disorders in football players was conducted until several prominent NFL players retired from the game with lingering and unresolved neurologic sequelae from recurrent mild traumatic brain injuries (concussions). Since then multiple studies have raised concerns about the longer-term health effects of recurrent concussions. Research based on autopsy data has identified chronic traumatic encephalopathy (CTE) as a pathologically distinct neurodegenerative condition affecting a wide range of individuals, including football players, who have experienced multiple concussions. Terms are retired from the progressive decline in neuron functioning occurring years or

Podcast



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decades after exposure to repetitive concussive injuries and presents clinically as progressive neurologic dysfunction affecting mental status, balance, and movement.⁸

The purpose of this article is to report the results of an analysis of NFL player mortality from neurodegenerative disorders including Alzheimer disease (AD), Parkinson disease (PD), and ALS. It is not possible to directly examine mortality from CTE because the pathologic refinement of the CTE diagnosis has only occurred within the last few years, and CTE is not listed as a cause of death in any revision of the International Classification of Diseases (ICD). As an alternative, because it is now known that neurologic conditions previously attributed to AD, PD, and ALS may actually have been related to CTE,4,9 an analysis that combined all neurodegenerative causes of death was conducted; this analysis included deaths that may be related to CTE even if not reported as such on death certificates.

METHODS Full details of the cohort have been described previously. 1,10 In brief, the cohort includes 3,439 NFL players identified by a pension fund database of vested players with at least 5 credited playing seasons between 1959 and 1988. Vital status was ascertained from pension fund records, the Social Security Administration, and the Internal Revenue Service. Players were matched to the National Death Index (NDI) beginning in 1979 (when the NDI began) with follow-up through 2007. The NDI provided underlying and contributing causes of death, coded to the ICD revision in effect at the time of death. Death certificates were obtained from state vital statistics offices and were coded by a certified nosologist when death information was not provided by the NDI.

Mortality was analyzed using the NIOSH life table analysis system (LTAS.NET).¹¹ Analyses used US male mortality rates (1960–2007) for 119 cause of death categories.¹² Mortality for 3 neurodegenerative causes of death was evaluated using updated custom rate files.¹³ Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were adjusted for race, age (in 5-year categories), and calendar year (in 5-year categories). Because AD and PD are more likely to be listed as a contributing cause than as the underlying cause, additional analyses used multiple cause of death (MCOD) rate files to examine all causes listed on the death certificates. Good candidates for MCOD analyses are diseases of long duration, not necessarily fatal, that are serious enough to be noted on the death certificate.¹⁴

Recent studies suggested that football players who play certain positions are at higher risk of concussion because of the high acceleration, rotational acceleration, and multiple impacts they experience during games. 15,16 Data collected using exposure assessment methods including video analysis, simulation and reconstruction techniques, and helmet-mounted accelerometers suggest that although linemen experience the highest number of head impacts, other positions experience higher acceleration impacts that result in concussions. 16–18 To examine possible neuro-

logic mortality differences from the high acceleration head impacts, we stratified the players into 2 categories based on position played¹⁰ (identified using annual data compiled in commercial publications): speed (quarterback, running back, halfback, fullback, wide receiver, tight end, defensive back, safety, and linebacker) and nonspeed (all defensive and offensive linemen); punters and kickers were excluded from the stratified analysis. LTAS.NET was used to calculate directly standardized rate ratios (SRRs) and 95% CIs for the neurodegenerative causes using the nonspeed players as an internal referent; 95% CIs that excluded unity were considered to be statistically significant.

Standard protocol approvals, registrations, and patient consents. The protocol for this study was approved by the NIOSH Institutional Review Board and has been assigned approval number HSRB 06-DSHEFS-04XP.

RESULTS Approximately 39% of the cohort is African American, and 62% played speed positions (table 1). African American players comprise almost half (48%) of the speed stratum but only 28% of the nonspeed stratum. There were minimal differences between the strata for all other cohort characteristics. The cohort is relatively young (median age of 57 at date last observed), and only 10% are deceased.

Compared with that of US men, the overall mortality in the cohort was significantly reduced (table 2); however, mortality was significantly elevated for all neurodegenerative causes combined and for the subclassifications of AD (when all causes on death certificates were considered) and ALS. Mortality from PD was elevated but did not reach statistical significance. Overall, results based on all contributing causes were similar to results based on underlying causes with the exception of AD, which was more likely to be listed as a contributing cause rather than the underlying cause on death certificates. Neurodegenerative mortality stratified by speed position considered all death certificate causes (table 3). Compared with those for US men, SMRs for the speed positions were significantly elevated for all neurodegenerative causes combined, AD, and ALS, but not for PD. Neurodegenerative mortality was not elevated for the nonspeed positions. Compared with the nonspeed positions, mortality was nonsignificantly elevated for the speed positions for all neurodegenerative causes combined, AD, and ALS, but not for PD. These results were highly imprecise because of the small numbers.

DISCUSSION Although the overall mortality of this cohort is significantly lower than expected (SMR 0.53), the neurodegenerative mortality is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an in-

Table 1 Characteristics of the National Football League Players Cohort, overall and by position category (1960–2007)^a

Characteristic	Overall (n = 3,439)	Speed (n = 2,145)	Nonspeed (n = 1,166)
Race, n (%)			
White	2,070 (60) ^b	1,111 (52)	835 (72)
African American	1,355 (39)	1,029 (48)	323 (28)
Other	14 (<1)	5 (<1)	8 (1)
Vital status as of December 31, 2007, n (%)			
Alive	3,105 (90)	1,972 (92)	1,014 (87)
Dead	334 (10)	173 (8)	152 (13)
First credited season			
Median (range)	1973 (1950-1984)	1974 (1950-1984)	1972 (1950-1984)
<1980, n (%)	2,685 (78)	1,654 (77)	930 (80)
≥1980, n (%)	754 (22)	491 (23)	236 (20)
No. credited seasons (as of 1988/1989 season), median (range) $^{\rm c}$	8 (5-25)	7 (5-21)	8 (5-20)
Age at death, y, median (range)	54 (27-81)	54 (27-80)	53 (29-81)
Age at date last observed, alive			
Median (range)	57 (45-88)	56 (45-82)	57 (45-83)
<50 y, n (%)	633 (20)	409 (21)	203 (20)
50-54 y, n (%)	738 (24)	502 (25)	208 (21)
55–59 y, n (%)	565 (18)	338 (17)	206 (20)
60-69 y, n (%)	890 (29)	552 (28)	300 (30)
≥70 y, n (%)	279 (9)	171 (9)	97 (10)

^a Player position was collapsed into 2 strata for analysis purposes: speed positions (fullback, halfback, defensive back, quarterback, wide receiver, running back, linebacker, and tight end) and nonspeed positions (defensive end/lineman/tackle, guard, nose guard, tackle, center, and offensive end/guard/lineman/tackle). Punters and kickers are included in the overall results only.

creased risk of neurodegenerative disease among football players.

It is not possible to determine from our study what has caused this increased risk. Research suggests that football players who have experienced one or more concussive blows to the head are at increased risk of neurologic disorders. In retired professional players, one study observed a 5-fold prevalence of mild cognitive disorders and a 3-fold prevalence of significant memory problems for players who experienced 3 or more concussions compared with players with fewer than 3 concussions.³ Excess neurologic mortality and morbidity has also been reported in players of other sports for which head impacts and concussion are common: soccer, boxing, horse racing, and hockey.¹⁹

Studies that examined the incidence of concussion in football players found that players in speed positions experienced concussions more commonly than players in nonspeed positions. Speed players are those who are able to build up considerable momentum before the point of being tackled or tackling another player. 15,17,20 Offensive and defensive linemen (nonspeed players)

usually engage other players soon after the football is snapped, thus mitigating the potential to build up momentum before a tackle or a block. 15,16

Although our study used causes of death from AD, PD, and ALS as reported on death certificates, recent research now suggests that CTE may have been the true primary or secondary factor in some of these deaths. Whereas CTE is a clinically distinct neurologic diagnosis, CTE symptoms are often similar to those found in patients with AD, PD, and ALS.^{6,21} In addition, CTE is not listed as a distinct cause of death recognized in current or previous ICD revisions, precluding the calculation of CTE-specific results. To account for possible misclassification, we reported combined results for all neurodegenerative causes.

Our study had several limitations. Our analysis is based on a few neurodegenerative deaths; therefore, the confidence intervals surrounding our SMR and SRR values are relatively broad. The few deaths also limited our ability to stratify players into more than 2 broad position categories; therefore, we were not able to identify potentially important differences in neu-

^b Percentages may not sum to 100% due to rounding.

^c Number of credited seasons does not necessarily equal the number of seasons played.

Table 2 Overall mortality, selected causes, National Football League Players Cohort (1960 – 2007)

	Underlying	ja	Contributi	ng ^b
Cause of death	No.	SMR (95% CI)	No.	SMR (95% CI)
All deaths	334	0.53 (0.48-0.59)	782	0.54 (0.51-0.58)
All cancers	85	0.58 (0.46-0.72)	122	0.63 (0.53-0.76)
All cardiovascular diseases	126	0.68 (0.56-0.81)	340	0.71 (0.64-0.79)
All neurodegenerative causes	10	2.83 (1.36-5.21)	17	3.26 (1.90-5.22)
Dementia/Alzheimer disease ^c	2	1.80 (0.22-6.50)	7	3.86 (1.55-7.95)
Amyotrophic lateral sclerosis ^d	6	4.04 (1.48-8.79)	7	4.31 (1.73-8.87)
Parkinson disease ^e	2	2.14 (0.26-7.75)	3	1.69 (0.35-4.94)
All injuries	41	0.63 (0.45-0.86)	57	0.69 (0.52-0.89)
Violence	13	0.27 (0.14-0.46)	13	0.26 (0.14-0.45)
All other causes	59	0.34 (0.26-0.43)	233	0.37 (0.33-0.42)

Abbreviations: CI = confidence interval; ICD = International Classification of Diseases; SMR = standardized mortality ratio (US referent rates).

rodegenerative mortality risk across the various positions included within the speed position group.

Because our cohort was limited to longer-term professional players, our findings may not be applicable to other professional or nonprofessional football players. However, recent autopsy studies have reported pathologic findings of CTE in college-age and professional football players with relatively short playing careers.²² We did not have data on player injuries or concussions. If chronic mild to moderate concussion is an actual risk factor for neurodegenerative mortality, the magnitude of the risk may depend

on the intensity and frequency of brain injuries incurred over a number of years. A few studies have attempted to measure these injuries for a limited number of players over a limited period of time but such measurements have proven to be difficult and underreporting is a problem.^{23,24} Finally, we did not have information on environmental, genetic, or other risk factors for neurologic disorders.

Although the results of our study do not establish a cause-effect relationship between football-related concussion and death from neurodegenerative disorders, they do provide additional support for the find-

Table 3 Mortality for neurodegenerative causes of death (considering all causes of death reported on the death certificate) stratified by position category, National Football League Players Cohort (1960–2007)

	Nonspeed ^a		Speed		
Cause of death	No.b	SMR (95% CI)	No.	SMR (95% CI)	Speed vs nonspeed: SRR (95% CI)
All neurodegenerative causes	3	1.58 (0.33-4.61)	14	4.74 (2.59-7.95)	3.29 (0.92-11.7)
Dementia/Alzheimer disease ^c	1	1.51 (0.04-8.41)	6	6.02 (2.21-13.1)	5.96 (0.72-49.6)
Amyotrophic lateral sclerosis	1	1.71 (0.04-9.50)	6	6.24 (2.29-13.6)	3.88 (0.47-32.2)
Parkinson disease	1	1.53 (0.04-8.53)	2	2.01 (0.24-7.25)	1.19 (0.11-13.2)

Abbreviations: CI = confidence interval; SMR = standardized mortality ratio (US multiple cause of death referent rates); SRR = directly standardized rate ratio (internal analysis).

^a Underlying indicates the number of deaths for which the cause was selected as the underlying cause of death on the death certificate.

^b Contributing indicates the number of times the cause appeared on the death certificate (i.e., underlying and contributing). ^c ICD-7 codes 304–305, ICD-8 codes 290.0–290.1, ICD-9 codes 290.0–290.3 and 331.0, and ICD-10 code G30; includes senile and presenile dementia but excludes cerebrovascular dementia because it is probably due to underlying cerebral vascular disease.

^d ICD-7 code 356.1, ICD-8 code 348.0, ICD-9 code 335.2, and ICD-10 code G12.2.

e ICD-7 code 350, ICD-8 code 342, ICD-9 code 332, and ICD-10 codes G20-G21.

^a Punters and kickers were excluded, and remaining player positions were collapsed into 2 strata for analysis purposes: speed positions (fullback, halfback, defensive back, quarterback, wide receiver, running back, linebacker, and tight end) and nonspeed positions (defensive and offensive linemen).

^b Number indicates the number of times the cause appeared on the death certificate (i.e., underlying and contributing causes).

^c Includes senile and presenile dementia but excludes cerebrovascular dementia.

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ing that professional football players are at an increased risk of death from neurodegenerative causes. Additional studies to quantify the cumulative effects of brain injuries, in particular the relative effects of concussive-level injuries, will be of particular importance in understanding the underlying disease mechanisms.

AUTHOR CONTRIBUTIONS

Study concept and design: E.J. Lehman, M.J. Hein. Acquisition of data: S.L. Baron, C.M. Gersic. Study coordination: C.M. Gersic. Analysis and interpretation of data: E.J. Lehman, M.J. Hein, S.L. Baron. Drafting/revising manuscript: E.J. Lehman, M.J. Hein, S.L. Baron, C.M. Gersic. Critical revision of the manuscript for important intellectual content: E.J. Lehman, M.J. Hein, S.L. Baron. Statistical analysis: E.J. Lehman, M.J. Hein. Obtain funding: E.J. Lehman. Administrative, technical, or material support: E.J. Lehman, C.M. Gersic. Study supervision: E.J. Lehman, S.L. Baron.

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DISCLOSURE

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Neurodegenerative causes of death among retired National Football League players

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EXHIBIT 19

The New York Times



SOCCER | NYT NOW

Brain Trauma Extends Reach Into Soccer

Researchers Find Bellini, Star for Brazil, Had Brain Disease C.T.E.

By SAM BORDEN SEPT. 23, 2014

> Bellini, a Brazilian soccer star who led the team that won the 1958 World Cup and was honored with a statue outside the Estádio do Maracanã in Rio de Janeiro, had a degenerative brain disease linked to dozens of boxers and American football players when he died in March at age 83.

At the time, his death was attributed to complications related to Alzheimer's disease. But researchers now say he had an advanced case of chronic traumatic encephalopathy, or C.T.E., which is caused by repeated blows to the head and has symptoms similar to those of Alzheimer's.

C.T.E. can be diagnosed only posthumously, and few brains of former soccer players have been examined. Bellini is the second known case, according to Dr. Ann McKee, a neuropathologist at Boston University and the Veterans Affairs Medical Center in Bedford, Mass., who assisted in examining Bellini's brain. McKee was also involved this year when researchers found C.T.E. in the brain of a 29-year-old man from New Mexico who had played soccer semiprofessionally.

McKee said in an interview that she was aware of a third former soccer player who had C.T.E. but that she was not yet authorized to publicly identify the person.

As C.T.E. began to gain widespread attention about six years ago, it was often thought of as an American problem. Many of the early cases of the disease, for which there is no known cure, were connected to boxers and

American football players.

But more recently, evidence has mounted to indicate that those at risk for developing C.T.E. include soccer players. McKee said that although it was too early to say whether heading of balls was a cause of C.T.E. in soccer, it was becoming apparent that players were at risk of long-term brain trauma.

"I think there's been a perception that the nonhelmeted sports are somehow less likely or less prone to these kinds of diseases," she said. "There was also a time when people said C.T.E. was only an American problem. I think we are learning that, in both cases, those things aren't true, and this is a problem that is going to be seen around the world."

Dr. Lea T. Grinberg, a neuropathologist specializing in brain aging who has been affiliated with the University of São Paulo and is an assistant professor at the University of California, San Francisco, led the study of Bellini's brain and presented her analysis recently at the International Congress of Neuropathology in Brazil.

In her remarks, Grinberg raised concerns about risks in soccer, including those that come with heading the ball.

"The Brazilian almost learns to walk and play football at the same time, so you need to learn more about it," Grinberg said, according to a report in the newspaper O Globo. "Do we need to concern ourselves with weekend recreational players? And do children, who have a more fragile neck, have more risk? We do not have those answers yet."

McKee noted that while outward symptoms of C.T.E. are similar to those of Alzheimer's, the initial diagnosis of Alzheimer's in Bellini was incorrect; a brain exam showed no evidence of Alzheimer's. Rather, Bellini had what McKee described as Grade 4 C.T.E., the most severe level of injury.

In Bellini's case, there were multiple symptoms. A halfback who was Brazil's captain when it won its first World Cup in 1958, Bellini first began to struggle with memory loss nearly 20 years ago, his wife, Giselda, told O Globo, recalling an instance when he failed to bring home items from a shopping list. The problems worsened, she said, in 2006.

Once, she told the paper, Bellini hired a taxi and asked the driver to take him to the home base of a São Paulo soccer team he had played for decades earlier, because he believed he needed to go to training.

McKee said she had been told that Bellini was not known to have sustained any nonsoccer head injuries in his life.

A version of this article appears in print on September 24, 2014, on page B11 of the New York edition with the headline: Brain Trauma Extends Reach Into Soccer.

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EXHIBIT 20

Forbes

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MoneyBuilder

We help you make sense of your finances.

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PERSONAL FINANCE 7/27/2011 @ 6:50PM 21,021 views

How Many Times Will You Crash Your Car?



This post provided by CarInsurance.com

If you haven't been in a car accident, consider yourself lucky. Or overdue.

By <u>car insurance</u> industry estimates, you will file a claim for a collision about once every 17.9 years. That's if you're an average driver, which, whether you're willing to admit it or not, you likely are.



Click for full photo gallery: 10 Used Cars to Avoid

So if you got your license at age 16, the odds are quite good that you'll experience some kind of crash by the time you're 34, at the latest. Over the course of a typical long, driving lifetime, you should have a total of three to four accidents.

Chances are these crashes won't be deadly. There are about 10 million accidents of all kinds each year, from parking lot scrapes to multi-car pileups, according to the National Safety Council; in 2009, just three of every 1,000 of those accidents involved fatalities.

But these crashes most likely will be costly. More than 2 million people are injured in crashes every year. In 2010, the average claim for injuries to cover both the insured driver and others involved in the crash had risen to \$23,450, thanks in large part to soaring medical costs, according to the Insurance Research Council, a nonprofit research group. (See "<u>The safest ways to get 40 mpg</u>.")

Accidents on the installment plan

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Which brings us to why this little-known number is so critical. (We got the accident-every-18-years statistic from the Property Casualty Insurers Association of America, a trade association that analyzes insurance data.)

Insurance companies may sell protection — and one night of TV advertisements suggests that they do a pretty good job on this front — but they're in the game to make a profit. And they don't make a profit by paying for your accidents. They do so by getting *you* to pay for your accidents — in advance.

"You're paying a smaller portion over a longer period of time," explains Dee Dee Mays, an actuary with Perr&Knight, an insurance consultancy. "It's kind of a way to spread your risk."

How to price your <u>insurance rates</u> low enough to lure you from a competitor, but high enough to make a profit on your future accidents, involves elaborate risk assessments that constitute the secret sauce of the insurance business.

Computer data can now create thousands of driver-profile combinations. But all can be boiled down to the need to determine two things:

- How many accidents will occur? Or, put another way, how likely is each driver in each car to have an accident? And,
- · How much will each accident cost?

You're already a statistic

7/2/2014

How often you're considered due for that next accident depends a little, too, on your insurer. A company that insures large numbers of young drivers — who are far more likely to have accidents — will likely budget for a shorter gap between crashes. State Farm, the country's largest auto insurance company, has customers with slightly lower-than-average accident rates.

"If we just take collisions, the average State Farm policy holder has a collision claim once every 19 years," says State Farm spokesman Dick Luedke.

But odds are made to be beaten, right?

Many factors are beyond a driver's immediate control. Clearly you can't alter road conditions or medical costs, at least by the time your insurance bill is due. That, in the insurance game, makes you a firm stat: a driver paying for the accident he's expected to have every 17.9 years.

But there are some ways you can move the needle, ways that will both change your lifetime-accident rate and lower your insurance premium.

Assuming that, at least today, you can't change your age, your driving history, or what kind of car you drive, here are some behaviors you can incorporate to lower your accident risk and, in the end, your insurance rates.

Don't drive impaired. No single factor is more likely to cause an accident than a driver impaired by alcohol or other drugs. One-third of fatal accidents in this country are attributed to drunken drivers alone.

Don't drive during the vampire hour. The deadliest three-hour periods on American roadways are between midnight and 3 a.m. on Saturdays and Sundays, according to the National Highway Traffic Safety Administration (NHTSA). Of those fatal crashes, 66% involve alcohol-impaired driving.

Keep your eyes on the road. NHTSA data show that 995 of the 30,797 fatal crashes in 2009 involved drivers using cell phones. Nearly, 5,500 traffic deaths involved a driver distracted by something inside the car, including technology, according to the U.S. Department of Transportation

Don't speed. Nearly one-third of all fatal accidents are attributed to speeding or driving too fast for conditions. Speeding is the single greatest contributor to accidents other than impaired driving. Insurance companies love such proven risk factors when assessing rates. Anyone who's seen their premiums skyrocket after getting a ticket knows this well.

Avoid congestion. Less than a quarter of both injury crashes and non-injury crashes in 2009 occurred on roadways with a posted speed limit of 55 mph or higher. Fewer intersections apparently make for fewer crashes. Be careful, though: When accidents do occur on these highways, they are more likely to be deadly, accounting for nearly half of all traffic fatalities.

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EXHIBIT 21



Traumatic brain injury may be an independent risk factor for stroke

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Traumatic brain injury may be an independent risk factor for stroke

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ABSTRACT

Objective: To explore whether traumatic brain injury (TBI) may be a risk factor for subsequent ischemic stroke.

Methods: Patients with any emergency department visit or hospitalization for TBI (exposed group) or non-TBI trauma (control) based on statewide emergency department and inpatient databases in California from 2005 to 2009 were included in a retrospective cohort. TBI was defined using the Centers for Disease Control definition. Our primary outcome was subsequent hospitalization for acute ischemic stroke. The association between TBI and stroke was estimated using Cox proportional hazards modeling adjusting for demographics, vascular risk factors, comorbidities, trauma severity, and trauma mechanism.

Results: The cohort included a total of 1,173,353 trauma subjects, 436,630 (37%) with TBI. The patients with TBI were slightly younger than the controls (mean age 49.2 vs 50.3 years), less likely to be female (46.8% vs 49.3%), and had a higher mean injury severity score (4.6 vs 4.1). Subsequent stroke was identified in 1.1% of the TBI group and 0.9% of the control group over a median follow-up period of 28 months (interquartile range 14–44). After adjustment, TBI was independently associated with subsequent ischemic stroke (hazard ratio 1.31, 95% confidence interval 1.25–1.36).

Conclusions: In this large cohort, TBI is associated with ischemic stroke, independent of other major predictors. **Neurology® 2013;81:1-7**

GLOSSARY

 ${f CI}={f confidence}$ interval; ${f ED}={f emergency}$ department; ${f HCUP}={f Healthcare}$ Cost and Utilization Project; ${f HR}={f hazard}$ ratio; ${f ICD}{ extbf{-9}{ extbf{-CM}}}={f International}$ Classification of Diseases, ninth revision, Clinical Modification; ${f OR}={f odds}$ ratio; ${f SEDD}={f State}$ Emergency Department Databases; ${f SID}={f State}$ Inpatient Databases; ${f TBI}={f traumatic}$ brain injury.

Ischemic stroke and traumatic brain injury (TBI) are common,^{1,2} costly,^{3,4} and leading causes of severe disability in adults.^{1,5} In particular, both stroke and TBI are responsible for substantial disability in working-age adults—approximately 20% of strokes⁶ and more than 40% of TBI⁷ occur in adults younger than 65 years.

In the recent past, no specific stroke mechanism was identified for many strokes in the young.⁸ Although the proportion of unexplained stroke may be decreasing based on more recent data,⁹ a large proportion of stroke risk is unexplained by the frequently used stroke prediction models.¹⁰ Identifying novel risk factors has the potential to improve stroke prevention and outcomes. TBI is a potential unrecognized stroke risk factor as trauma to the head and neck may increase stroke risk through vascular dissection,¹¹ microvascular injury, or abnormal coagulation.¹²

A recent observational study in Taiwan based on administrative data¹³ suggested an association between TBI and all stroke types. However, the association was strongest for known components of TBI (subarachnoid and intracerebral hemorrhage), and a large proportion of stroke risk occurred in the first month. Therefore, it is possible that some events classified as incident stroke were merely sequelae of the TBI and that the magnitude of the observed association may have been overstated.

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Casea18-2012mdD000179ehB 000118341658201-Pagee6520/06Date Filed: 308/09/2019

In the current study, we explored whether the findings in the Taiwanese study extend to a representative region in the United States while limiting to cases of ischemic stroke and accounting for additional confounders. In secondary analyses, we explored whether the TBI-stroke relationship differed by severity of trauma, subtype of TBI, and when excluding early recurrent stroke.

METHODS This retrospective cohort study was based on emergency department (ED) visits and inpatient discharges for the state of California from 2005 to 2009 from the State Inpatient Databases (SID),¹⁴ State Emergency Department Databases (SEDD),¹⁵ Healthcare Cost and Utilization Project (HCUP), and Agency for Healthcare Research and Quality. SID and SEDD capture all inpatient discharges and all ED visits that do not result in admission, respectively, within a given year. California was selected for this analysis because of its large population and because it allows for linkage of SEDD and SID records over multiple years using HCUP revisit files.¹⁶ We compared TBI patients with non-TBI trauma patients (controls) while accounting for a variety of other variables that may confound the association between TBI and ischemic stroke.

Standard protocol approvals, registrations, and patient consents. The study protocol, which does not rely on human subjects, was deemed not regulated by the University of Michigan Institutional Review Board because it relied on private coded information that cannot be linked to specific individuals by the investigators.

Patient selection. Adults 18 years or older were entered into our cohort if they survived either an inpatient admission (SID) or an ED visit (SEDD) for TBI or trauma at any time from 2005 to 2009. TBI was defined using the Centers for Disease Control and Prevention criteria: ICD-9-CM 800.0-801.9, 803.0-804.9, 850.0-854.1, or 959.01 in any discharge diagnosis field.^{17,18} Our TBI definition was designed to maximize differentiation of TBI and non-TBI trauma. Trauma is inherently a multisystem process, so limiting our diagnosis to only a subset of TBI claims (e.g., principal diagnoses only) would risk misclassifying patients with new TBI as non-TBI trauma. The non-TBI trauma group was composed of patients who had a fracture, excluding fractures of the head and neck: ICD-9-CM 807.0-807.9, 812-819.9, 822-822.9, or 823-827.9 in any position on the discharge record. If a patient had both TBI and non-TBI trauma codes or separate visits with both TBI and non-TBI trauma, they were classified as TBI. Individuals with a visit (ED or inpatient) with stroke (ICD-9-CM 433.x1, 434.x1, 436)19 before TBI or trauma were excluded from the cohort. Similarly, if a patient had multiple TBI or non-TBI trauma visits, they were entered into the cohort with their first visit. In addition, given the known role of arterial dissection as a mediator of ischemic stroke risk in trauma patients, we excluded all patients with carotid (ICD-9-CM 433.21) or vertebral (433.24) dissection at the index visit (n = 66).

Outcome. Our primary outcome was any hospitalization with a discharge diagnosis of ischemic stroke: *ICD-9-CM* 433.x1, 434. x1, and 436 from 2005 to 2009.¹⁹ This combination of diagnosis codes has been previously validated relative to medical record review and found to have a positive predictive value of 90% and sensitivity of 86%.²⁰ ED visits that did not result in admission for ischemic stroke were not included in the primary outcome because of concerns about the accuracy of coding.

Covariates. Our primary analysis adjusted for known and possible stroke predictors including demographics, vascular risk factors, comorbidities, trauma severity, and trauma mechanism. Age was divided into quartiles because of the known nonlinear relationship between age and stroke.1 Vascular risk factors were defined using the HCUP single-level clinical classification system.²¹ Comorbidities were defined based on diagnosis codes listed on the discharge record using the modified Charlson definition, and all Charlson comorbidities were included in our model.²² Trauma severity was estimated with the Abbreviated Injury Scale (ICD/AIS)²³ using the software package ICDMAP-90²⁴—a validated algorithm for assigning trauma severity using ICD-9 codes.25 Mechanism of trauma was accounted for by including major external cause of injury group codes (E codes), which describe the intent, mechanism, and circumstances of injuries independently of the anatomical location of an injury. 26,27

Primary analysis. Demographics and baseline characteristics of the TBI and the non-TBI trauma groups were summarized using descriptive statistics. Subsequent stroke was compared by TBI status with Kaplan-Meier estimates and the log-rank test. We were unable to determine whether a patient died outside the context of a hospitalization and thus cases were not censored at death. Cumulative hazard of stroke was estimated at different time intervals using the Nelson-Aalen method and the differences in cumulative hazard were calculated. Confidence intervals (CIs) of the differences were estimated using bootstrapping.

Our primary adjusted analysis relied on Cox proportional hazards modeling.²⁸ We examined the association of TBI and stroke after adjusting for demographics, payer, vascular risk factors (hypertension, hyperlipidemia, diabetes, atrial fibrillation), all Charlson comorbidities, trauma severity, whether a patient had multiple visits for trauma/TBI, and trauma mechanism, while accounting for clustering at the hospital level. To explore how covariate groups (demographics, comorbidities, vascular risk factors, trauma severity, trauma mechanism) affected the TBI-ischemic stroke association, we also developed models in which covariate groups were added serially. Given the increased incidence of epilepsy in patients with TBI²⁹ and the potential for misdiagnosing seizure as stroke,³⁰ we included a covariate that represented whether a patient had any ED visit or admission for epilepsy (ICD-9-CM 345.x) or convulsions (780.3x).31 The proportional hazards assumption central to Cox modeling was tested by visually inspecting plots of the cumulative hazards function and plots of Schoenfeld residuals and no violations of the proportional hazards assumption were found.32

Secondary analyses. We performed a series of post hoc secondary analyses to assess the robustness of the association between TBI and ischemic stroke that either added covariates to our primary analysis or stratified our primary analysis on covariates of interest. First, to determine whether there was a relationship between specific TBI types and ischemic stroke, we analyzed the risk of ischemic stroke for TBI subtypes identifiable by ICD-9-CM codes: skull fracture (800-801.9, 803-804.9), concussion (850-850.9), cerebral laceration/intracranial hemorrhage (851-853.9), other intracranial injury (854-854.9), and unspecified TBI (959.01).33 Second, to assess whether the TBI-ischemic stroke association may differ depending on overall trauma severity, we repeated our primary analysis stratified over injury severity tertiles. In addition, to assess for possible missed early stroke diagnosis (i.e., stroke present at initial trauma/TBI presentation and not diagnosed at that time), we repeated our primary analysis excluding all ischemic stroke hospitalizations that occurred within 7, 30, or 60 days of trauma. Next, to characterize the relative temporal association between TBI and stroke, we repeated our

Table 1 Baseline patient characterist	e 1 Baseline patient characteristics			
	No TBI (n = 736,723)	TBI (n = 436,630)		
Demographics				
Age, y, mean (SD)	50.3 (20.1)	49.2 (22.4)		
Female, n (%)	363,210 (49.3)	204,298 (46.8)		
Race/ethnicity, n (%)				
White	426,587 (57.9)	251,095 (57.5)		
African American	43,418 (5.9)	31,003 (7.1)		
Hispanic	136,908 (18.6)	80,753 (18.5)		
Asian	24,879 (3.4)	22,111 (5.1)		
Other	104,931 (14.3)	51,668 (11.8)		
Insurance, n (%)				
Medicare	190,409 (25.9)	120,571 (27.6)		
Medicaid	72,680 (9.9)	43,502 (10.0)		
Private	287,086 (39.0)	150,909 (34.6)		
Self-pay	107,268 (14.6)	73,755 (16.9)		
Other/missing	79,280 (10.8)	47,893 (11.0)		
Vascular risk factors, n (%)				
Hypertension	125,752 (17.1)	75,438 (17.3)		
Hyperlipidemia	41,206 (5.6)	20,873 (4.8)		
Diabetes	59,141 (8.0)	31,897 (7.3)		
Coronary artery disease	24,930 (3.4)	16,573 (3.8)		
Peripheral vascular disease	6,151 (0.8)	3,045 (0.7)		
Atrial fibrillation	14,702 (2.0)	12,359 (2.8)		
Comorbidities, a n (%)				
Congestive heart failure	15,505 (2.1)	9,133 (2.1)		
Dementia	5,061 (0.7)	5,504 (1.3)		
Chronic obstructive pulmonary disease	34,775 (4.7)	17,129 (3.9)		
Rheumatologic disease	4,915 (0.7)	2,092 (0.5)		
Peptic ulcer disease	1,473 (0.2)	724 (0.2)		
Mild liver disease	5,618 (0.8)	3,760 (0.9)		
Renal disease	13,538 (1.8)	7,386 (1.7)		
Cancer	5,064 (0.7)	3,385 (0.8)		
Severe liver disease	849 (0.1)	627 (0.1)		
Metastases	1,617 (0.2)	1,154 (0.3)		
HIV/AIDS	490 (0.1)	330 (0.1)		
Epilepsy ^b	7,997 (1.1)	14,798 (3.4)		
History of multiple trauma/TBI°	103,090 (14.0)	69,863 (16.0)		
Admission characteristics				
Admitted, n (%)	167,406 (22.7)	80,264 (18.4)		
Injury severity, ^d mean (SD)	4.1 (3.6)	4.6 (10.1)		

Abbreviation: TBI = traumatic brain injury.

primary analysis by including only strokes that occurred in the first year after the index event and then again by excluding all strokes that occurred within the first year. We also explored the role of age on the TBI-stroke association by stratifying our analysis at age 50 years. In addition, to assess for alcohol and drug abuse/dependency as possible mediators of the relationship between TBI and ischemic stroke, we repeated our primary analysis adjusting for any alcohol/drug abuse diagnoses (ICD-9-CM 291-292.9, 303-304.9). Finally, to assess for the role of other potential stroke risk factors (e.g., vasculitis) and risk factors that are suboptimally measured (e.g., smoking³⁴), we repeated our primary analysis and estimated the stroke-TBI association after adjusting for the following: hypercoagulable disorders, prior venous thromboembolism, obesity, vasculitis, arrhythmias other than atrial fibrillation, valvular disease, patent foramen ovale, and smoking.

RESULTS The study cohort included 1,173,353 total trauma subjects, 436,630 (37%) with TBI. The median duration of follow-up was 28 months (interquartile range 14–44), with a total of 11,229 (1%) ischemic strokes identified during this timeframe—1.1% in the TBI group and 0.9% in the non-TBI trauma group. The patients with TBI were slightly younger than controls (mean age 49.2 vs 50.3 years), less likely to be female (46.8% vs 49.3%), and had a higher mean injury severity score (4.6 vs 4.1). Further details of the study population are summarized in table 1.

Association between TBI and ischemic stroke hospitalization.

Kaplan-Meier survival curves for survival free from ischemic stroke after TBI and non-TBI trauma are illustrated in the figure. The TBI group was more likely to be hospitalized for ischemic stroke than the non-TBI trauma group (log-rank test, p < 0.01). The difference between the unadjusted Nelson-Aaler cumulative hazard function in the TBI group compared with the non-TBI trauma group was 0.07% (0.06%–0.09%) at 90 days and 0.21% (0.18%–0.24%) at 2 years.

After adjustment for all covariates (table 2), TBI was associated with ischemic stroke hospitalization (hazard ratio [HR] = 1.31, 95% CI 1.25–1.36). This association only changed slightly when covariate groups were serially added: demographics only (HR = 1.34, 95% CI 1.28–1.39), addition of vascular risk factors (HR = 1.30, 95% CI 1.25–1.35), addition of comorbidities (HR 1.30, 95% CI 1.25–1.35), and addition of injury severity and trauma mechanism (HR = 1.31, 95% CI 1.25–1.36).

Secondary analyses. The association between TBI and ischemic stroke hospitalization was robust in that similar associations were observed under a variety of different modeling assumptions (table 3). All TBI subtypes had a similar magnitude of association with ischemic stroke, and when stroke hospitalization within 7, 30, 60, or 365 days of trauma was excluded from the outcome measure, the ischemic stroke—TBI association only modestly decreased (table 3). The

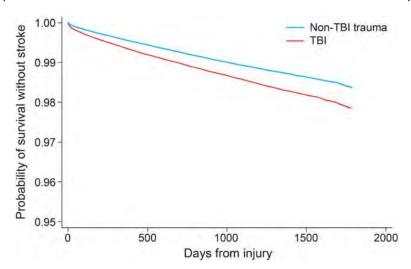
^a Defined using the modified Charlson definitions.

^b Defined as *ICD-9-CM* 345.x or 780.3x.

 $^{^{\}rm c}$ Defined as positive if a patient had multiple prior admissions or emergency department visits for trauma during the cohort.

^d Assessed using the Abbreviated Injury Scale (ICD/AIS).





Note that these curves are presented to demonstrate the likely minimum difference in stroke risk between TBI and non-TBI trauma patients. The absolute risk estimates from this curve may be inaccurate because of lack of death censoring (see Discussion section). Log-rank test: p < 0.00001.

age-stratified analysis was a secondary analysis in which the stroke-TBI association was most substantially altered, with a greater association observed in the population younger than 50 years (odds ratio

Table 2 Cox model output Hazard ratio (95% CI)^a p Value Age, y, reference 18-32 33-48 5.32 (4.26-6.64) < 0.01 49-66 16.3 (13.1-20.3) < 0.01 67+ 37.3 (29.7-46.9) < 0.01 Female 0.98 (0.94-1.03) 0.48 Race/ethnicity, reference white African American 1.69 (1.56-1.83) < 0.01 Hispanic 1.08 (1.01-1.15) 0.03 Asian 0.88 (0.80-0.97) 0.010.97 (0.90-1.04) 0.36 Vascular risk factors/comorbidities Hypertension 1.34 (1.28-1.40) < 0.01 Hyperlipidemia 0.91 (0.86-0.97) < 0.01 Diabetes 1.33 (1.26-1.40) < 0.01 Coronary artery disease 1.11 (1.04-1.23) < 0.01 Peripheral vascular disease 1.11 (1.00-1.23) 0.05 Atrial fibrillation 1.76 (1.65-1.88) < 0.01 1.47 (1.34-1.61) < 0.01 **Epilepsy** 1.00 (1.00-1.01) 0.60 Injury severity 1.31 (1.25-1.36) < 0.01

Abbreviations: CI = confidence interval; TBI = traumatic brain injury.

[OR] 1.56, 95% CI 1.32–1.85) vs the population 50 years and older (OR 1.22, 95% CI 1.16–1.28).

DISCUSSION We found a robust association between TBI visits and subsequent hospitalization for ischemic stroke in California from 2005 to 2009, even after adjusting for a number of potential confounding variables. The magnitude of this association was substantial (HR 1.31) and was similar to the association between the leading stroke risk factor, hypertension (HR 1.34), and ischemic stroke. Given the higher prevalence of TBI in this trauma population, TBI was responsible for more ischemic stroke than hypertension. The TBI-ischemic stroke association persisted in secondary analyses after accounting for a variety of variables and assumptions that may alter the stroke-TBI relationship. Despite the robust association of TBI and ischemic stroke, the absolute ischemic stroke risk difference between TBI and non-TBI trauma patients in this low-risk cohort is small. Nonetheless, if further research definitively established TBI as a novel stroke risk factor, this would stimulate research to understand stroke pathophysiology after TBI and inform stroke prevention efforts in this young population with few vascular risk factors.

We found a similar association between ischemic stroke and TBI as in the prior Taiwanese study.13 In our study, the association persisted after selecting non-TBI trauma controls that are likely more similar to the TBI population than the age- and sex-matched controls in the Taiwanese study. We also found that the ischemic stroke-TBI association was similarly unaffected by accounting for potential confounders such as trauma severity and trauma mechanism. Interestingly, we found that the difference in ischemic stroke risk between the TBI and non-TBI trauma groups was not just attributable to a high early risk in patients with TBI. The risk of stroke after TBI persisted even when excluding cases of stroke within 60 days of trauma. This finding differs somewhat from the prior Taiwanese study that found a large early recurrence rate and a more modest effect after 30 days. We also found that the TBI-stroke association was of considerably greater magnitude in the population younger than 50 years (OR 1.56) vs those 50 years and older (OR 1.22), suggesting that TBI may be uniquely important in younger patients.

If the association between TBI and ischemic stroke is causal, a number of potential pathways may explain this relationship. For example, TBI causes alterations in the coagulation cascade, which in turn may increase stroke risk. ¹² However, given that these alterations last briefly, they likely explain at most a portion of the association found in this study. TBI is also known to cause vascular dissection—a well-described ischemic stroke mechanism. ^{35,36} Our analysis excluded dissection-mediated

^a Hazard ratio for major risk factors and TBI after also adjusting for payer, all Charlson comorbidities, injury mechanism (E codes), whether the patient had multiple events, and whether the patient was admitted.

Table 3	Secondary analyses ^a	
		Hazard ratio (95% CI) for stroke after TBI
Baseline mo	odel	1.31 (1.25-1.36)
	odel limited to outcome of agnosis of stroke	1.29 (1.23-1.35)
Excluding e	pilepsy rather than adjusting for epilep	sy 1.31 (1.25-1.36)
Excluding a	II head/neck arterial injuries	1.29 (1.23-1.36)
Including al	cohol and drug-related dependency	1.30 (1.25-1.36)
Including at	typical stroke risk factors	1.29 (1.23-1.35)
Excluding s	troke within 7 d	1.27 (1.22-1.33)
Excluding s	troke within 30 d	1.25 (1.20-1.31)
Excluding s	troke within 60 d	1.25 (1.20-1.31)
Excluding s	troke within 1 y	1.24 (1.17-1.31)
Excluding s	troke after 1 y	1.38 (1.31-1.46)
Stratified b	y trauma severity	
Tertile 1	(lowest severity)	1.10 (1.01-1.20)
Tertile 2		1.29 (1.16-1.43)
Tertile 3	(highest severity)	1.25 (1.16-1.35)
Stratified b	y age	
<50 y		1.56 (1.32-1.85)
≥50 y		1.22 (1.16-1.28)
Using TBI s	ubtypes	
Skull frac	ture	1.21 (1.05-1.41)
Concussion	on	1.27 (1.17-1.37)
Intracran	ial bleeding	1.21 (1.12-1.31)
Other int	racranial injury	1.38 (1.07-1.76)
Unspecifi	ed	1.33 (1.27-1.40)

Abbreviations: CI = confidence interval; TBI = traumatic brain injury.

stroke; however, given the small number of dissections identified by claims, it is likely that some dissections were undetected. Dissection is unlikely, however, to explain the entire association given the relatively low long-term risk of ischemic stroke after dissection,³⁷ the high short-term recanalization rates after dissection,³⁸ and the fact that the risk difference between TBI and non-TBI trauma patients appears to continue to increase even years after the initial injury. Although other novel pathophysiologic pathways may have a role, it is also possible that patients with TBI may accrue conventional vascular risk factors at a faster rate than patients with non-TBI trauma because of a more sedentary lifestyle after TBI.

This study has a number of important limitations. First, inaccuracy in administrative diagnosis coding may affect both stroke and TBI diagnoses. For example, sequelae of TBI could lead to a misdiagnosis of ischemic stroke based on neuroimaging studies. If this was the case, we would have expected a stronger association between TBI and ischemic stroke in any position on the record compared with the association between TBI and ischemic stroke as the principal diagnosis because principal position diagnoses generally have a higher specificity.³⁹ However, we found a similar association between TBI and stroke regardless of the stroke's position on the claim, thus suggesting that the results are not attributable to diagnostic inaccuracy. Similarly, it is possible that patients presenting with focal neurologic symptoms after a seizure related to their TBI are misdiagnosed with stroke.³⁰ However, our primary analysis adjusted for patients with any epilepsy diagnosis and in secondary analyses we excluded these patients, but the TBI-ischemic stroke association was not substantially affected. Similar potential limitations exist for claims-based diagnosis of mild TBI, which is relatively specific but insensitive.33 As a consequence, some of the patients in our non-TBI trauma control group likely had TBI. To the extent that this was the case, we would have expected the relationship between TBI and ischemic stroke to be biased toward the null. Similarly, because the control group may also be susceptible to an increased stroke risk relative to the general population (e.g., mediated through lack of mobility), it is possible that the reported association between TBI and stroke represents an underestimate. In addition, our estimates of the risk of ischemic stroke in both the TBI cases and controls are underestimates because we were unable to capture out-of-state stroke hospitalizations or to account for competing mortality. We do not expect, however, that either of these limitations would explain our primary findings. First, we were able to account for risk of mortality after trauma using the injury severity score. Second, TBI patients in general would be expected to have a higher mortality than non-TBI trauma patients⁴⁰; therefore, failing to account for competing mortality would likely lead to underestimation of the true TBIischemic stroke association. As with all observational studies, unmeasured confounders (e.g., differences in baseline medications) may lead to biased estimates. Finally, this dataset enables only limited inferences about the possible mechanistic links between TBI and trauma given that many of clinical details (e.g., ischemic stroke subtype, localization, severity) are not measured.

TBI is associated with ischemic stroke, and further work is needed to assess whether it may be a novel stroke risk factor. Prospective cohort and/or population-based, cross-sectional studies are needed to confirm the association, explore potential mechanisms for the association

^a The top portion of the table shows the magnitude of the TBI-ischemic stroke association in our baseline model and in 5 additional models that accounted for possible confounders between the TBI-stroke association (misdiagnosis of epilepsy, alcohol/drug dependency, missed stroke diagnosis at the time of initial presentation, and atypical or poorly measured stroke risk factors [hypercoagulability, obesity, prior venous thromboembolism, vasculitis, any arrhythmia, endocarditis, any valvular abnormality, patent foramen ovale, and smoking]). The middle portion of the table shows the TBI-ischemic stroke association in analyses stratified by trauma severity. The bottom portion of the table demonstrates the association between TBI subtypes and ischemic stroke.

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between TBI and ischemic stroke, and carefully characterize the clinical features of both TBI and subsequent stroke, including both TBI and stroke mechanism, size, and location.

AUTHOR CONTRIBUTIONS

Dr. Burke drafted the initial manuscript, participated in development of study design, performed the primary data analysis, and acquired the data. Dr. Stulc and Dr. Skolarus revised the manuscript for content, participated in development of the study design, and participated in data interpretation. Dr. Sears revised the manuscript for content, participated in development of the study design, and participated in data analysis. Dr. Zahuranec revised the manuscript for content, participated in development of the study design, and participated in data interpretation. Dr. Morgenstern revised the manuscript for content, initially developed the study concept, participated in formulation of the study design, and participated in data interpretation.

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DISCLOSURE

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Traumatic brain injury may be an independent risk factor for stroke
James F. Burke, Jessica L. Stulc, Lesli E. Skolarus, et al.

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CRITICAL REVIEW

Neuropsychology and clinical neuroscience of persistent post-concussive syndrome

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Abstract

On the mild end of the acquired brain injury spectrum, the terms concussion and mild traumatic brain injury (mTBI) have been used interchangeably, where persistent post-concussive syndrome (PPCS) has been a label given when symptoms persist for more than three months post-concussion. Whereas a brief history of concussion research is overviewed, the focus of this review is on the current status of PPCS as a clinical entity from the perspective of recent advances in the biomechanical modeling of concussion in human and animal studies, particularly directed at a better understanding of the neuropathology associated with concussion. These studies implicate common regions of injury, including the upper brainstem, base of the frontal lobe, hypothalamic-pituitary axis, medial temporal lobe, fornix, and corpus callosum. Limitations of current neuropsychological techniques for the clinical assessment of memory and executive function are explored and recommendations for improved research designs offered, that may enhance the study of long-term neuropsychological sequelae of concussion. (JINS, 2008, 14, 1–22.)

Keywords: Concussion, Mild TBI, Biomechanics, Neuroimaging, Neuropathology, Neuropsychology

INTRODUCTION: BRIEF HISTORY OF CONCUSSION

That concussion occurs and is commonplace is not in dispute. The United States Government's Center for Disease Control (CDC) estimates that there are more than one million concussions that occur annually in the United States, using their definitional statement of concussion being a condition "of temporarily altered mental status as a result of head trauma (www.cdc.gov, see Rutland-Brown et al., 2006)."

What is controversial is whether one fully recovers without symptoms from having sustained a concussion. Given the commonness of concussions along with the adaptive nature of brain function combined with neural plasticity (Duffau, 2006; Giza & Prins, 2006; Moucha & Kilgard, 2006; Priestley, 2007), it might be assumed that any transient impairment as a result of concussion would not result

in any neurological sequelae. Indeed, historically the original Latin term "commotio cerebri" was used to describe concussion, thought to occur because of "traceless disturbances" that produced momentary functional impairment without any damage to brain tissue (see reviews by McCrory & Berkovic, 2001; Vos et al., 2002) . Hence, for decades, one of the venerable definitions in standard neurology textbooks, exemplified by the following quote from Grinker's Neurology was as follows: "the usual patient loses consciousness briefly, soon recovers and thereafter is without symptoms" (Vick, 1976; p. 651). In that concussion was thought to be mostly benign, the non-biological and psychodynamic theories that dominated the beginnings of clinical psychology and psychiatry minimized the effects head injury could have on behavior. This is captured by the 1947 quote by Page (1947) in an abnormal psychology textbook that "Head injuries and gunshot wounds involving damage to the brain occasionally produce mental disturbances, but such injuries are not an important cause of mental disease (p. 330)". Persistent maladaptive symptoms in this time frame were believed to be more an expression of a "neurosis" than anything possibly "organic." So,

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"persistent" problems following concussion were interpreted within a psychogenic framework. In fact, one of the most cited publications in the clinical literature on concussion is that of Miller (1961) whose series of articles centered on the theme of concussion being nothing more than "Accident Neurosis", which others have labeled as "Compensation Neurosis" (Levy, 1992) because of the prevalence of lawsuits involving mild head injury (Hall & Chapman, 2005; Mooney et al., 2005). No doubt "psychological" factors play an important role in the residuals from concussion (Meares et al., 2006; Whittaker et al., 2007; Wood, 2007), but they and other "functional" factors are also the source of intense debate and controversy over the existence of post-concussive symptomology (Cantu, 2007; Evans, 1994; King, 2003). These controversies will be discussed in greater detail later in this review.

Part of this controversy has to do with nomenclature and definition. Years ago, Vick (1976) also stated that terms like concussion are "... of little value" because of "such wide and indefinite connotations" (p. 650). Much has been written about the definition of concussion (Blostein & Jones, 2003; Boake et al., 2005; Ruff & Jurica, 1999), including the definitional statements by major organizations and consensus panels as presented in Table 1, wherein the terms concussion and mild traumatic brain injury (mTBI) are used interchangeably. For this review, in referring to studies, if the authors used the term concussion then that term will be used in referring to the study and likewise, if the term mTBI is used by the authors, that term will be used; otherwise, mTBI and concussion will be used interchangeably in the current review. However, this review focuses on the persistence of symptoms following concussion or what has been referred to as post-concussive syndrome (PCS), but this term then brings up additional controversies. In the majority of those concussed, symptoms abate within minutes to hours to days post-injury. Thus, some refer to PCS if the symptoms persist for more than a few days and in particular, if the symptoms persist for more than a week (Anderson et al., 2006; Sheedy et al., 2006). If the symptoms last more than 3 months then the term persistent post-concussive syndrome or PPCS has been used (Begaz et al., 2006; Chamelian et al., 2004; Iverson, 2006; Rees, 2003; Satz et al., 1999; Stalnacke et al., 2005; Willer & Leddy, 2006). Whereas there is a relationship between severity of concussion and who develops PPCS (Hessen et al., 2006), concussion severity by itself is a poor predictor of who develops PPCS (Guskiewicz et al., 2004).

DSM-IV lists PCS as a disorder under its "research" classification and some have referred to it as a syndrome (King, 2003; Rees, 2003; Ryan & Warden, 2003) and there are differences in symptom criteria between DSM-IV and the International Classification of Disorders (ICD-10) that further cloud this taxonomy issue (Kashluba et al., 2006; McCauley et al., 2005). Whether PCS is a disorder or syndrome is another ongoing debate (Hall & Chapman, 2005; Smith, 2006). Neither DSM-IV or ICD use the PPCS label. Nosological issues are not the focus of this review and there

are several excellent recent reviews on this topic ((Hall & Chapman, 2005; Silver et al., 2005; Smith, 2006; Zasler et al., 2007). Thus, for the current review PPCS is operationally defined as symptoms that persist beyond three months following a concussion (having met at least one of the definitions as listed in Table 1), implicating chronic sequelae.

As demonstrated by Table 1, there are many definitional statements about what constitutes a concussion or mTBI. Neuropsychological research on this topic would be aided to have a universally accepted definition as the standard (see Tagliaferri et al., 2006). Nonetheless, all definitions in Table 1 have general agreement that "mTBI is defined as the consequence of blunt (non-penetrating) impact with sudden acceleration, deceleration or rotation of the head with a Glasgow Coma Score (GCS) of 13–15... (Vos et al., 2002, p. 207)." Thus, concussion occurs because of impact physical forces affecting the brain and if, physical forces are insufficient to injure the brain, no injury has occurred.

Regardless of the etiology, recovery from concussion is typically rapid and ostensibly complete in most individuals. Clearly, the best-controlled studies examining outcome following concussion, demonstrate good to complete recovery in the majority of individuals (Iverson et al., 2007). Additionally, at least with sports concussion, major consensus statements of the past five years have resulted in statements like "concussion typically results from the rapid onset of short lived impairment of neurological function that resolves spontaneously" and that "concussion may result in neuropathological changes but the clinical symptoms largely reflect a functional disturbance rather than structural injury" as reviewed by (Cantu, 2007, p. 963). So this review focuses on the *minority* of subjects who sustain a concussion, who remain symptomatic after three months. Large-scale studies demonstrate approximately 70% of all head injury cases seen in the emergency room (ER) are in the mTBI category (Udekwu et al., 2004). However, as pointed out by the CDC and other studies (Delaney et al., 2005), a substantial number of concussions is never evaluated in the ER, making it difficult to obtain precise numbers as to the true annual incidence rate. Bazarian et al. (2005) estimate that the annual mTBI incidence rate is 503.1/100,000, of which PPCS rates have been conservatively estimated at 10% (Ruff et al., 1996; Wood, 2004). Thus, despite the overall good to complete recovery rates from concussion, this remains a major public health concern (Langlois et al., 2005) and the field of neuropsychology should better understand the disorder (Kelly, 1999; Langlois et al., 2005).

From a neuropsychological standpoint, symptoms of impaired attention, memory, and executive function along with changes in emotional regulation dominate the clinical picture of PPCS (Lundin et al., 2006). An objective of this review is to understand these features in terms of a common pathological basis. To accomplish this, how evolutionary factors may have shaped recovery from concussion, followed by an up-to-date review of important new studies on the biomechanics of concussion and a thorough discussion

Table 1. The Multiple Definitions and Grading Systems of Concussion

Concussion Grading Systems						
Grade	Cantu	Colorado	Roberts	American Academy of Neurology		
0			"Bell ringer"; no LOC; no PTA			
1	No LOC; PTA <30 min	No LOC; confusion without amnesia	No LOC; PTA <30 min	No LOC; transient confusion; concussion symptoms or mental status abnormality resolve in <15 min		
2	$\label{eq:LOC} \begin{split} LOC < &5 \text{ min; PTA} > 30 \text{ min} \\ \text{and } < &24 \text{h} \end{split}$	No LOC; confusion with amnesia	LOC <5 min; PTA >30 min and <24h	No LOC; transient confusion; concussion symptoms or mental status abnormality last >15 min		
3	LOC >5 min or PTA >24h	LOC	LOC >5 min or PTA >24h	Any LOC, either brief or prolonged		
LOC = lo	ss of consciousness; $PTA = post-trav$	imatic amnesia (from Lecler	rc et al., 2001)			

2^{nd} International Conference on Concussion in Sport, Prague 2004

(1) "Concussion may be caused by a direct blow to the head, face, neck or elsewhere on the body with an 'impulsive' force transmitted to the head. (2) Concussion typically results in the rapid onset of short lived impairment of neurological function that resolves spontaneously. (3) Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury.(4) Concussion results in a grade set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. (5) Concussion is typically associated with grossly normal structural neuroimaging studies. Two Classifications of Concussion: (1) Simple Concussion—In simple concussion, an athlete suffers an injury that progressively resolves without complication over 7–10 days." (2) "Complex Concussion—Complex concussion encompasses cases where athletes suffer persistent symptoms (including persistent symptom recurrence with exertion), specific sequelae (such as concussive convulsions), prolonged loss of consciousness (more than one minute), or prolonged cognitive impairment after the injury" (p. 196–197) (McCrory et al., 2005)

European Federation of Neurological Societies—2002 Task Force

"mTBI is defined as the consequence of blunt (non-penetrating) impact with sudden acceleration, deceleration or rotation of the head with a GCS scores of 13–15 on admission to hospital (p. 209).

Mild	Category	GCS	Clinical Description	*Risk Factors	
	0	15	No LOC, no PTA, = head injury, no TBI. No risk factors*	Unclear or ambiguous accident history, continued post-traumatic amnesia, retrograde amnesia longer	
	1	15	LOC < 30 min, PTA $< 1 hr No risk factors*$	than 30 min, skull fracture, severe headache, vomiting,	
	2	15	GCS = 15 + Risk factors present*	ent* focal neurological deficit, seizure, age < 2 years,	
	3	13–14	LOC < 30 minutes, PTA < 1 hr. With or without risk factors present* (Vos et al., 2002)	$\label{eq:age} \mbox{age} > 60, \mbox{coagulation disorders, high energy accident,} \\ \mbox{intoxication with alcohol/drugs}$	

American Congress of Rehab Medicine Definition

A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function as manifested by at least one of the following:

- (1) Any period of loss of consciousness;
- (2) Any loss of memory for events immediately before or after the accident;
- (3) Any alteration in mental state at the time of the accident (e.g. feeling dazed, disoriented or confused)
- (4) Focal neurological deficit(s), that may or may not be transient but where the severity of the injury does not exceed the following:
 - (A) loss of consciousness of approximately 30 minutes or less;
 - (B) after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13-15; and
 - (C) post-traumatic amnesia (PTA) not greater than 24 hours. (American Congress of Rehabilitation Medicine Head Injury Interdisciplinary Special Interest Group, 1993)

The WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury (mTBI)

"mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare, These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g., psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury, p. 115). (Carroll et al., 2004a)

[&]quot;Sports concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathological, and biomechanical injury constructs that may be used in defining the nature of a concussive head injury include the following:

of what is now currently known about the neuropathological and pathophysiological basis of concussion will be offered. The last part of the review will focus on more traditional neuropsychological concepts as they relate to concussion and conclude with suggestions on improved research tactics on this topic. There may be nothing more controversial in contemporary clinical neuropsychology, than the issues to be discussed in this review. At the outset, these controversies are acknowledged and the approach of this review is to first overview the contemporary neuroscience of concussion and deal with the most controversial issues at the end of the review.

EVOLUTIONARY ASPECTS OF INJURY

Undoubtedly concussions have been part of mammalian life since the beginning. The universality of concussions is that the stunned, motorically wobbly appearance commonly observed in an athlete, particularly a boxer who has been concussed, is replicated with animal models (Shaw, 2002). Survivability across mammalian species following concussion is testament to the fact that most concussions are but transient disruptions in normal brain function allowing the animal (including humans) to recover quickly and fully return to pre-injury abilities and activities. Because of the commonness of concussions, it is likely that genes that promoted certain brain morphologies and/or positive recovery characteristics have been passed down. However, concussions prior to the modern era would have occurred only from falls, falling or thrown objects, fisticuffs, combat, and the like. All of these remain major sources of concussions but with the modern era, concussions also occur from highspeed impacts that simply were never the source of injury in earlier times. So, whatever evolutionary advantages occurred they did so prior to the modern era. Likewise, genes selective for their ability to promote survivability of a brain injury were most likely only associated with simple concussion and not more severe brain injury, because prior to modern medical treatment the majority of moderate-tosevere injuries would not have been survivable or lead to disability that could not be sustained.

From a structural standpoint, the position of the irregular skull base to the dural surface of the frontal and temporal lobes, housed with in the anterior and middle cranial fossa provides a means for holding the brain in position, in response to movement and/or mild trauma to the head (Bigler, 2007). Likewise, the position of the ventricles dissipates some of the strain effects with movement, including that of concussion (Ivarsson et al., 2002). Both of these have significant evolutionary advantage. It is also very likely that a selective bias occurred that favored rapid brain reparative mechanisms once a concussion occurred (Diaz-Arrastia & Baxter, 2006). In fact the most common of injuries for a particular organ system are the very ones most likely shaped by evolution (Martin & Leibovich, 2005). So key to recovery from concussion is a fast acting reparative system and this would emphasize a transient cellular response that immediately re-establishes neural homeostasis. In addition to reparative metabolic and cellular responses, redundancy and back-up neural circuitry activated once a primary system were injured would be critical to recovery (Bach-y-Rita, 2004; Desmurget et al., 2007; Duff, 2001; Guigon et al., 2007; Kercel et al., 2005). These redundant systems can either share in or take over function for injured neurons and networks. A neural systems reserve capacity probably directly relates to how rapid recovery from brain injury occurs, including concussion (Berker, 1996; Stern, 2007) and the role of genes in this recovery process is being examined (Alexander et al., 2007; McAllister et al., 2006)

One final evolutionary speculation will be made and that is based on the appearance and "design" of the fornix (see Fig. 1), the major white matter output from the hippocampus. At least half of the fornix is suspended beneath the corpus callosum and loosely connected with the septum pellucidum as it dives toward its connection with the mammillary body and septum (Andersen et al., 2006). One look at this delicate anatomical structure and it is obvious that it was not selected for its ability to withstand brain trauma. Evolutionarily, in lower mammals the fornix is clearly imbedded in brain parenchyma, but moving up the evolutionary tree with the expansion of the cerebral hemispheres, and the ventricular system, the fornix becomes more progressively suspended (see Crosby & Schnitzlein, 1982). The importance of the hippocampus and fornix in understanding mTBI is a major part of this review.

Physics of TBI

Given that concussions are so commonplace it *must* be easy to at least transiently impair the brain through mechanical deformation and there *must* be common neurological structures affected [see Figs. 1 and 2; (Ropper & Gorson, 2007)]. In a most innovative experiment by Bayly et al. (2005) human volunteers were studied using MRI to determine momentary brain parenchymal deformation when the head falls just 2 cm. MRIs of the brain were obtained before and immediately after the drop, comparing the degree of brain deformation or warping by measuring changes in fixed points between the two scans. These movements were far below the threshold for concussion and the authors liken this to the type of head (and brain) acceleration when jumping vertically a few inches and landing flat-footed. The authors estimated that it was 10% to 15% of the acceleration of "heading" a soccer ball. However, even with this mild impact the brain deforms. Bayley et al.'s conclusions were as follow: "When the skull decelerates, the brains center of mass continues to move, but the motion of the base of the brain appears constrained near the sellar and supra-sellar space. Tethering loads may be borne by the vascular; neural; and dural elements, which bind the brain to the base of the skull. Such anatomic structures might include the distal internal carotid arteries, the optic nerves, the olfactory tracts, the oculomotor nerves, and the pituitary stalk. All these structures pass through fixed bony or dural rings, which

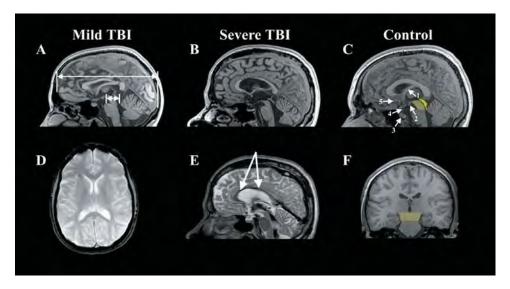


Fig. 1. The top row presents mid-sagittal T1 MRIs comparing the fornix and corpus callosum from a control (C) to that observed in mTBI (A) and severe TBI (B). The control figure is labeled where the following structures are identified: (1) fornix, (2) mammillary body (3) pituitary, where it is situated in the sella turcica, (4) hypophysis of pituitary stalk, and (5) region of the basal forebrain. The light yellow depicts the region of the tegmentum of the midbrain (shown in coronal view in F), whereas the darker yellow represents the tectal region of the midbrain. The coloration of the midbrain is also done to highlight the relative smallness of the mibrain compared to the size of the cerebrum, and how the cerebrum 'rests' atop the midbrain. As shown in (A) from the patient with mTBI, the length of the cerebrum (long arrow) is approximately 10 times the length of the midbrain (short arrow). (D) depicts an axial gradient recall echo (GRE) depicting multiple deposits (black dots) of hemosiderin in the frontal region, implicating shear injury, note how they are mostly located at the gray-white matter junction. This patient had sustained an mTBI in a MVA. Note that there is thinning of the corpus callosum and a shear lesion in the isthmus region. (E) is a T2 mid-sagittal MRI depicting extensive hemosiderin deposition along the body of the corpus callosum (arrows) and also note the generalized atrophy of all structures in the severe TBI case compared to the mTBI and control.

restrict their movement. These features attach to or penetrate the more mobile brain parenchyma. As a result, the brain begins to rotate about this region, while material anterior is compressed and material posterior is stretched by initial effects. As the brain rotates backward and upward relative to the skull, the superior-frontal surface of the brain appears to compress against the top of the cranial vault. Normal forces, tangential forces, and possibly tension in the bridging veins on the superior surface of the brain eventually arrest the rotation of the brain in front of the superior contact region is compressed and pushed forward. Behind the superior points of contact, the brain is elongated as the brains inertia pulls it backward and clockwise. Finally, behind the basal tethering region, material in the brainstem experiences shortening and shear as the posterior and inferior parts of the brain continue rotating downward and forward (p. 852)." Bayly et al. (2006) have also performed this type of modeling on the rat pup brain with similar findings of significant transient mechanical deformation of the brain.

Viano et al. (2005b) used a different approach by simulating movement within the cranium by a "finite element analysis using a detailed anatomic model of the brain and head accelerations from laboratory reconstructions of game impacts (p. 891)" based on National Football League (NFL)

players who experienced on the field concussions that were videotaped. The exceptional innovativeness of this study was the ability to model the brain, including white and gray matter, the ventricular system, meninges, and in particular the falx cerebri and tentorium cerebelli along with the skull (most of these anatomical regions are shown in Figs. 1 and 2). In a number of those concussed, the initial strain occurred in the temporal lobe adjacent to the impact and then migrated though the temporal lobe to other brain regions. This is depicted in Figure 3. In *all* subjects concussed the largest strains that occurred in the migration of the brain deformation occurred in the fornix, midbrain and corpus callosum. Dizziness correlated with early strain in the orbital-frontal cortex and temporal lobe.

The Viano et al. (2005b) modeling study found, in general, excursions of the concussed brain to be between 3–6 mm at 24–26 ms post-impact. Of particular importance to neuropsychology is that this modeling shows 4–5 mm displacements of the hippocampus, caudate, amygdala, anterior commissure, and midbrain (again refer to Fig. 2). In addition to these brain regions showing significant displacement, they also related to various cognitive and physical symptoms from concussion in this group of NFL players. Also, increased strain at the level of the hypothalamus was associated with at least transient cranial nerve symptoms.

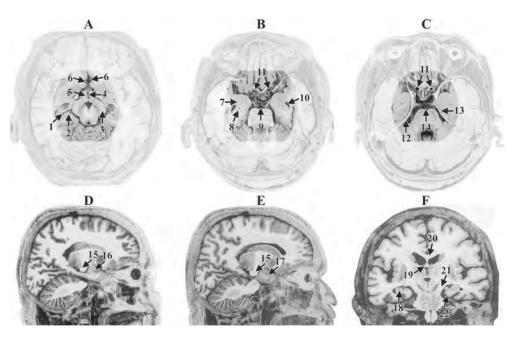


Fig. 2. All views are post-mortem, adapted from Mai et al. (2004) (and used with permission from Elsevier). A, B, and C represent axial views where the highlighted area represents some of the common regions where the greatest strain effects were demonstrated in the Bayly et al. (2005) and Viano et al. (2005b) studies. (A) 1—hippocampus, 2-subiculum, 3-cerebral peduncle, 4-III ventricle, 5—hypothalamus, 6—anterior cerebral artery, (B) 7—amygdala, 8—hippocampus, 9—basilar artery, 10—temporal horn of the lateral ventricle, 11—internal carotid arteries, (C) 12—free-edge of the tentorium, 13—entorhinal cortex, 14—basilar artery, P = pituitary in the position of the sella turcica. D and E are sagittal views: 15—cerebral peduncle, 16—amygdala, 17 temporal pole and F is a coronal view: 18—hippocampus, 19—fornix, 20—corpus callosum, (21) cerebral peduncle, and 22—entorhinal cortex adjacent to the free-edge of the tentorium. Note the closeness of all of these regions and any movement, lifting or twisting of the brain at its base would simultaneously affect all of these structures.

The models described earlier occur in well-controlled experimental conditions. Obviously, high speed impact head injuries are not a controlled experiment and likely involve more significant pressure and shear-strain forces than what are seen in sports concussion (Bradshaw et al., 2001; Zhang et al., 2006a). Regardless of these factors, the same brain regions as described earlier and as shown in Figures 1 and 2 are likely involved in all concussions, just a matter of degree. Similarly, much of the cognitive and neurobehavioral symptoms of concussion can be explained by the involvement of the brain regions highlighted in Figures 1 and 2. In these Figures, note the proximity of the medial temporal lobe to the midbrain, the fact that the free-edge of the tentorium makes contact with the medial temporal lobe and midbrain as well as the nearness of the basal forebrain to these regions along with the hypothalamus, hypophysis and pituitary stalk, and the arterial vasculature. So, within a few centimeters are critical brain structures that, if affected, could represent the structural basis to many symptoms associated with concussion.

Pathophysiology of Concussion

Iverson (2005) and Hovda (2004) provide an excellent and detailed reviews of the pathophysiology of concussion, which

need not be re-elaborated here. Whereas initiated by immediate biomechanical forces, as describe above, much of the pathology of acute concussion is believed to be transient biochemical induced neurotransmitter disruptions initiated within 25–50 msec of impact. Tensil forces also disrupt the cytoskeletal status of the axon and its ability to function, including disrupted axonal permeability and transport (Povlishock & Katz, 2005). Disrupted cytoskeletal architecture, renders cells less functional and may have widespread effects on the injured brain (Hall et al., 2005), albeit transient in concussion.

Since the Iverson (2005) and Hovda (2004) publications there are several important studies that add to our understanding of the potential microscopic pathology that can occur from concussion. Zetterberg et al. (2006) examined cerebrospinal fluid (CSF) taken by from lumbar puncture in 14 amateur boxers 7 to 10 days and 3 months after a bout compared to matched controls without any contact. They used several markers of neuronal and astroglial injury that can be readily detected in the CSF, finding significant indicators of neuronal injury byproducts in CSF that were positively related to the actual number of hits during a bout, most apparent in the initial samples taken after the amateur boxing contest. None of the boxers received a knock-out punch and likely did not meet any of the behavioral criteria

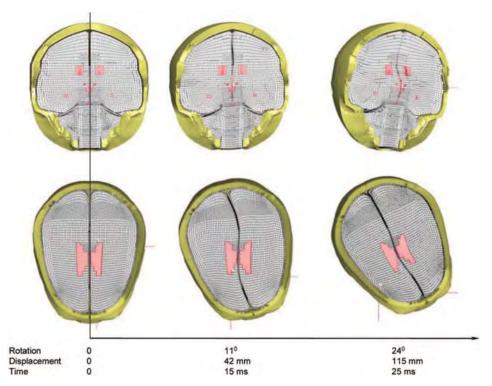


Fig. 3. From Viano et al. (2005b) published with permission from Lippincott Williams & Wilkins. The model on the left represents a coronal (top) and axial (bottom) view of the tagged brain model with the ventricle in pink and the skull encasing in yellow. The left hand column represents the baseline, where no movement occurred; notice the midline is vertical in the coronal plane and straight in the axial plane. Time in msec is shown on the x-axis. By 25 msec the model indicates that this player's brain had a maximal shift, where it is evident that there is particular distortion in the medial temporal and hypothalamic region. This was from a player concussed on a kick return who had brief LOC, and PCS symptoms of headache, fatigue, dizziness, and photophobia and sleep disorder as physical symptoms. Note that the modeling of this subjects brain would involve all of the structures identified in Figure 1, and indeed, the high strain findings modeled in this subject supported such a locus of injury (see Appendix 1B of the Viano et al., 2005b paper that detail individual characteristics of the subjects).

for concussion. This study confirms the presence of acute pathological changes in the brain that can occur from boxing, in blows to the head that are below the threshold for producing what behaviorally would be classified as a concussion in these conditioned athletes.

Using a different approach, Zhang et al. (2006b) examined conventional MRI along with diffusion tensor imaging (DTI) in a group of professional boxers. While the majority had normal clinical imaging, 7 of the 42 examined had abnormal white matter findings, which should not be evident in an otherwise young, healthy subjects (Hopkins et al., 2006). More importantly, even those without clinical abnormalities as a group exhibited DTI differences from their matched controls, suggesting subtle white matter abnormalities, particularly at the level of the corpus callosum. Recall that Viano et al. (2005b) showed that the corpus callosum was one of the brain regions receiving the biggest strain effect in concussion. Similarly, Chappell et al. (2006) using DTI methods demonstrated similar white matter pathology in a group of 81 professional boxers. These studies focused on professional boxers without known neurological impairment, otherwise they would not be boxing, and show that sensitive MRI methods do detect with a higher frequency abnormalities of white matter. Along these lines Cohen et al. (2007) have shown MR spectroscopic and subtle brain volume loss in mild TBI. Such imaging findings demonstrate that pathological changes in brain parenchyma can be detected in mild TBI using contemporary neuroimaging methods.

Bigler (2004) demonstrated hemosiderin and residual inflammatory reaction in the post-mortem brain of an individual with PPCS, where the autopsy was performed seven months post-injury. Similar findings were observed in a post-mortem of a professional football player who had developed cognitive decline later in life (Omalu et al., 2005). Combining the imaging and neuronal injury biomarker studies discussed earlier, with the Bigler (2004) and Omalu et al. (2005) post-mortem studies provide indisputable evidence that structural pathology can be present in mTBI. Additionally, these type of hemorrhagic lesions can be observed with specialized high-field MRI studies (see Ashwal et al., 2006; Scheid et al., 2006) as shown in Figure 4. As such, some aspects of the so-called "traceless injury" of concussion are being revealed with newer techniques.

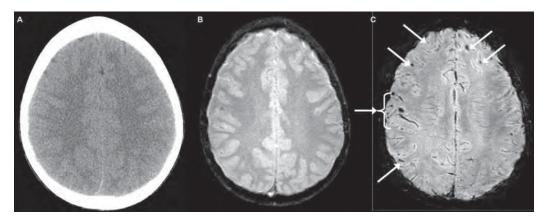


Fig. 4. This 12 year-old male had sustained a concussion in a skate-boarding accident. Eyewitness accounts estimate LOC to be approximately 7 minutes, but in the ER the patient was alert and not amnesic. However, because of the positive LOC a CT scan was performed (A), followed by the more routine GRE sequence (B) which revealed only a hint of hemosiderin deposition, however, the susceptibility-weighted sequence (C) clearly demonstrated multiple foci of hemosiderin deposition (see arrows). (Reproduced by permission from Jill Hunter, M.D., Texas Children's Hospital, Houston, Texas).

What is the significance of these pathological residua in those concussed, even when ostensibly reparative and restorative mechanisms return function to apparent baseline? Are there still potential sequelae that can be elicited and are these expressed overtime? Do these lesions relate to neuropsychological function? What Gronwall and Wrightson (1975) demonstrated years ago suggested that concussion may not be as benign as Miller (1961) had implied, but may be very dependent on the cognitive demands placed on a patient. Routine cognitive tasks may be unaffected, whereas more complex functions affected. This has been revisited more recently by Chen et al. (2003) using functional brain imaging in a small group of subjects (N = 5) who had sustained concussion, only two of whom had brief LOC (less than 2 minutes). In this study the concussed patients, none of whom were in litigation, all had neurobehavioral symptoms of PPCS, but their resting PET metabolism did not differ from controls. However, when given a spatial working memory task to perform, differences in regional cerebral blood flow were detected in prefrontal cortex in PPCS subjects. In other words, unless a significant cognitive demand was placed on the subject that required more than typical cognitive effort, no differences could be determined. Similarly, Bernstein (2002) demonstrated that by increasing the complexity of a dual task involving auditory and visual discrimination and measuring evoked responses that those with a history of concussion but ostensibly no residual complaints could be differentiated from controls (Dockree et al., 2006a).

Moreover, confirmation of the likely residual pathology from concussion is clearly demonstrated in the second-injury circumstance, where a prior concussion increases the likelihood of a second concussion and greater morbidity of the second concussion in both human and animal studies (Huh et al., 2007; Longhi et al., 2005; Manville et al., 2007; Moser et al., 2005; Omalu et al., 2005; Pellman et al., 2004;

Wall et al., 2006). The most straight forward explanation of the pathology of the second injury concussion is that the first concussion is simply not benign, but that the brain adapts quickly to the injury in most cases. It should be noted that there is some controversy over the second injury hypothesis (Iverson et al., 2006b; Schnadower et al., 2007) and much more animal and human research is needed to fully understand this phenomena (Laurer et al., 2001). From a clinical management standpoint, repeated concussions are the basis for recommendations to retire from sports (Cantu, 2003) and reported to be related to the presence of neuropsychiatric symptoms in professional North American Football players (Guskiewicz et al., 2007).

While petechial hemorrhage associated with concussion has been well documented neuropathologically for decades (Ashwal et al., 2006), the shearing phenomena may only be part of the pathological story of vascular injury in concussion. A most intriguing animal study by Ueda et al. (2006), inducing what would be at least a moderate brain injury, has shown that the perivascular nerve network is injured in TBI as well. It is often overlooked that there is a neural regulation of blood vessels and blood vessels can contract and expand under neurogenic control. In fact, it is the dispersion of blood in response to autoregulation and localized activation that is at the basis of functional neuroimaging. If a blood vessel has a subtle abnormality in its ability to regulate regional flow, this may contribute to the neuropsychological sequelae expressed in a concussed individual. This remains to be investigated and represents speculation at this time. Thus, in TBI the same mechanisms that stretch the neuron can stretch the blood vessel and this may impair the neurogenic response of the blood vessel. Thus, the functional neuroimaging findings in concussion may not just be a consequence of brain parenchymal injury, but vascular and blood-brain barrier disruptions (Korn et al., 2005).

Along these same lines, is how the peri-vascular spaces that house cerebral vasculature are affected by injury, because much of the surrounding tissue is white matter. Numerous studies have shown the vulnerability of white matter damage in TBI (de la Plata et al., 2007; Inglese et al., 2005a; MacKenzie et al., 2002) have all shown that in mTBI increased frequency of dilated perivascular spaces, changes in white matter volumetry and chemical composition occur and relate to persistence of symptoms. Significant inflammatory reactions and hemosiderin deposits occur in the perivascular space in response to injury and their presence is considered a marker of white matter injury (Beschorner et al., 2002; Konsman et al., 2007). What is potentially so important about these observations is that inflammatory reactions that may originally injure white matter parenchyma, at least experimentally, have been shown to disrupt dopaminergic function (Roy et al., 2007), which heuristically, could be the basis for some of the neuropsychiatric symptoms associated with damage to white matter.

Another neuropathological complexity that is only beginning to be understood is the individual differences and heterogeneity of injury to individual cells (Buki & Povlishock, 2006; Reeves et al., 2005; Singleton & Povlishock, 2004). This too may be under genetic control where individual differences to injury susceptibility relates to outcome. It just may be that certain neurons are more susceptible to injury and certain injury forces or dynamics than others (Park et al., 2006).

There are other biomarkers of injury that have also been examined in human mTBI. For example, Stalnacke et al. (2005), using a blood biomarker of brain injury, serum concentrations of S-100B and neuron-specific enolase, found that S-100B levels during the acute phase of mTBI related to long-terms sequelae. S-100B findings have not been universal in mTBI (see also Bazarian et al., 2006a; Bazarian et al., 2006b; De Kruijk et al., 2002; Savola & Hillbom, 2003) and these observations are but some of the first. The level of initial CSF tau, a microtubular binding protein, believed to be a marker of axonal injury, correlates with outcome in severe TBI (Ost et al., 2006), but it has not been systematically studied in mTBI.

Functional Neuroanatomy of Concussion and PPCS

In concussion, regardless of the definitional criteria used as outlined in Table 1 and the variability in clinical presentation, it is clear that 4 features dominate concussive symptoms—(1) brief alteration in consciousness or neurological function with at least acute changes in mentation and speed of processing; (2) physical symptoms of headache, dizziness and/or vertigo along with increased fatigability; (3) impairments in short-term memory, attention and concentration (particularly for multi-tasking); and (4) increased likelihood for changes in mood and emotional function. Where and how can these symptoms be integrated in understanding the functional neuroanatomy of

concussion? The assumption is that there must be a common origin to these symptoms.

Figure 1 is a sagittal MRI view of the brain. The average adult brain weighs somewhere between 1150 and 1450 grams (2.5–3 pounds), with most of that weight located in the cerebrum, above the cerebellum in the figure. The anterior aspect of midbrain region of the upper brainstem is comprised of the cerebral peduncles which house all of the major ascending and descending white matter pathways connecting the cerebrum with the periphery of the body and the connections between the cerebrum and the cerebellum. In an earlier review, these anatomic regions, pathway and structures have been outlined in detail (Bigler, 2007). As can be clearly visualized in the Figure 1, the midbrain at the level of the cerebral peduncle is small, opposed to frontaloccipital linear dimension, and in the vertical position the tegmental aspect of the upper midbrain "rests" on or is adjacent to the dorsum sellae and the anterior clinoid, partially shown in Figures 1 and 2. Just in front of the tegmentum is the hypophyseal fossa that house the infundibulum (or pituitary stalk), the neural connection between the ventral hypothalamus and the pituitary, situated in the sella turcica. Immediately lateral to the cerebral peduncle is the carotid groove of the sphenoid bone wherein the internal carotid artery ascends into the brain to form the anterior and medial cerebral arteries. Next, moving laterally just past the carotid groove is the inner edge of the greater wing of the sphenoid and the beginning medial surface of the temporal lobe (see Fig. 2). The entrance of internal carotid into the cranium through the carotid canal occurs just adjacent to the midbrain. What is particularly interesting about this region of the brain is that the tentorium cerebelli extends from a covering of the cerebellum to attach at the junction of the clinoid and lesser wing of the sphenoid. As the tenortium projects to its clinoid-lesser wing of the sphenoid connection, the lateral surface of the upper brainstem touches the "free edge" of the tentorium cerebelli, and just on the other side of the tentorium at this level is the medial surface of the temporal lobe, where the peririhinal and entorhinal surfaces also touch the "free edge" of the tentorium (Bigler, 2007; Van Hoesen et al., 1999). What is also of particular interest with regards to consciousness is that arterial branches of the posterior circulation of the brain actually cross the free edge of the tentorium and these arterial branches supply blood to the brainstem (Blinkov et al., 1992).

Biomechanics of concussion inform us that concussions are more likely to occur if there is some rotational force present (Fijalkowski et al., 2006; Viano et al., 2005a; Vorst et al., 2007). Returning to this midbrain region of the brain, if there is any stretching and/or rotational force at this level, note what occurs: the upper brainstem stretches across the clinoid and lesser wing of the sphenoid, with its lateral margins potentially striking the free-edge of the tentorium, the pituitary stalk stretches disrupting hypothalamic-pituitary connections, the internal carotid stretches against the carotid canal and posterior circulation to the brainstem is also dis-

rupted, the medial temporal lobe strikes the lateral surface of the free-edge of the tentorium as well as the medial wall of the sphenoid. Just in from this medial surface of the temporal lobe are the amygdala and hippocampus, with the hippocampus giving rise to the fornix that not only connects with the anterior thalamus via the mammillary body but also to the septum and pituitary (McDonald et al., 2006). Just anterior to the hypophysis-hypothalamic region is the basal forebrain; just posterior are the mammillary bodies. So at one level, if there is slight mechanical deformation either in terms of compression or uplift and particularly if rotation occurs, there are putative functional neuroanatomical connections disrupted for consciousness (upper brainstem, reticular activating system), memory (mechanical compression of perirhinal and entorhinal cortices disrupting input to the hippocampus or hippocampal output via the fornix and its connection with the anterior thalamus and cingulate), emotional regulation (medial temporal lobe and basal forebrain), post-traumatic migraine (stretching the internal carotid and all vasculature that forms the circle of Willis as well as stretching/irritation of the dura and other vessels) and fatigue as well as hormonal changes secondary to hypothalamic-pituitary disruption.

Indisputably, clearly demonstrated immediately after concussion (Barrow et al., 2006a; Barrow et al., 2006b), even in those who go on to fully recover, is slow speed of processing (Crawford et al., 2007; De Monte et al., 2005). Speed of processing is dependent on the integrity of white matter pathways maintaining their optimal inter-connectiveness. Returning to the biomechanical deformation effects reviewed above, long-coursing axons are going to be more vulnerable, particularly interhemispheric connections, especially the corpus callosum and anterior commissure (Cecil et al., 1998; Holshouser et al., 2006; Inglese et al., 2005b; Mathias et al., 2004; Wilde et al., 2006a; Wilde et al., 2006c). Thus, neuropsychological tasks that require interhemispheric integration and/or multiple intracortical connections often show differences in the form of slowed responding, even in those with mTBI (Mathias et al., 2004)

So, the hypothesis put forth in this section is that the biomechanics of brain injury simultaneously disrupt neurological function in the upper brainstem, pituitary-hypothalamic axis, medial temporal lobe, and basal forebrain concomitant with irritative injury to the vasculature and meninges, which gives rise to the symptoms observed in the post-concussive state and the neuropsychological sequela associated with such an injury. How rapidly these neural, dural, and vascular areas return to homeostasis or recovery from some adaptive mechanism or do not recover, provides the biological basis for the symptoms expressed.

Animal Models of Concussion

The advantage of animal models is the controlled environment where the reproducibility of an adverse effect can be tested, in this case a concussive brain injury. There have been numerous animal models of brain injury over the years (Leker et al., 2002), but most focused on what would be moderate-to-severe brain injury with focal cortical impact, producing not only focal brain injury but diffuse injury readily demonstrated by histological analysis. It has been challenging to develop an animal model of concussion that mimics human concussion, because of a host of differences associated with brain morphology, skull-brain interface, and species differences (Leker et al., 2002).

Nonetheless, several excellent animal models of concussive injury have recently been established (Gurkoff et al., 2006; Henninger et al., 2005; Milman et al., 2005; Tang et al., 1997; Tashlykov et al., 2007; Ucar et al., 2006; Yoshiyama et al., 2005; Zohar et al., 2003, 2006). For example, Henninger et al. (2005) modifying methods of Tang et al. (1997) have used a weight drop device to the exposed skull that replicates human concussion. As stated by these researchers, "immediately after impact, all TBI animals lost their muscle tone and righting reflex response (p. 450)" but it shortly returned. This is analogous to what is observed acutely in sports concussion (McCrory & Berkovic, 2000). After reflex recovery the concussed rats behaved "normally" in comparison to sham controls. In this study, memory was assessed using the Morris Water Maze (MWM), where the concussed animals also showed no differences from controls in ability to swim and other species typical behaviors. Thus, in terms of ordinary rat behavior, function returned without discernable abnormality following concussion. However, given time to heal from the minor surgery to expose the skull, the concussed animals exhibited memory deficits on the MWM when assessed nine days post-injury. This study also included high-field MRI which was negative. However, histology demonstrated several pathological changes including a reduction in the number of cortical neurons as well as in the hippocampus. A limitation of this study is that it only examined memory nine days postinjury but Milman et al. (2005) and Zohar et al. (2003, 2006) using somewhat similar methods, but in mice, have demonstrated these type of persistent cognitive differences in concussed animals for longer periods of time post-injury. Gurkoff et al. (2006) have demonstrated this in rats with a fluid percussion injury model and Tashlykov et al. (2007) have shown apoptotic changes in cerebral cortex and hippocampus using this weight drop technique as well.

So animal models of concussion do support the notion that persistent cognitive deficits can occur, although not all studies have found lasting effects (Gaetz, 2004; Leker et al., 2002). The difference between those studies that find persisting symptoms and those that do not is probably the severity of the concussion. For example, in the Tashlykov et al. (2007) study pellets of incremental weight from five to 30 g were dropped on the head of mice under light ether anesthesia. Of particular interest in this study is that *none* of the weight amounts produced any discernable change in the species typical behavior of the mice once recovered from the ether anesthesia, yet related to the weight amount of the pellet pathological changes were proportional to the impact. The 5 g weight drop was insufficient to produce any detect-

able pathological changes. A minimum of 10 g was necessary for showing pathological neuronal changes, but 15 g was necessary to initiate apoptotic changes. Thus, the threshold to produce injury varies depending on what pathological changes are under investigation and whether a certain injury threshold has been reached.

IS BRAIN INJURY ON A CONTINUUM: CONCUSSION → SEVERE TBI?

In examining the post-mortem brain of several human subjects who had sustained a "mild concussion," but died for reasons other than the head injury, Blumbergs et al. (1994) demonstrated presence of axonal injury, particularly in the fornix. Blumbergs et al. (1995) in a follow-up study demonstrated that the microscopic pathology was on a continuum from mild (GCS of 13-15) to severe (GCS of 3-8), again demonstrating the susceptibility of the fornix. As shown by Viano et al. (2005b), the fornix is distinctly vulnerable to the stress/strain effects of concussion and is a common area of damage in moderate-to-severe TBI, as visualized using MRI (Gale et al., 1995; Tate & Bigler, 2000; Tomaiuolo et al., 2004), where the degree of atrophy is related to severity of injury (Bigler et al., 2006; Tate & Bigler, 2000; Tomaiuolo et al., 2004; Wilde et al., 2006b). Because the fornix is a white matter structure containing projecting axons from the hippocampus, disruption in fornix integrity likely relates to the concussive effects of disrupted short-term memory, at least transiently.

At the histopathological level, severity can be graded by the degree of cell loss, cytoskeletal changes, presence of inflammatory cellular reaction, biochemical markers of cell damage or death, etc. and all seem to relate to severity on some continuum (Anderson et al., 2003; Vorst et al., 2007). Taken together, in well controlled animal models there is a continuum associated with severity of impact injury supporting the contention that injury is on a continuum (Gurkoff et al., 2006; Igarashi et al., 2007; Kharatishvili et al., 2006; Maegele et al., 2005; Ucar et al., 2006). Understanding this continuum means that at the mildest level of brain perturbation there may, in fact, be no lasting effect. However, once a threshold is reached, lasting sequelae begin to occur (Zhu et al., 2006).

Human neuroimaging studies also support the concept of continuum of injury. For example, a linear relationship with cerebral atrophy relates to injury severity measures such as GCS, PTA, and duration of LOC (Bigler et al., 2006; Wilde et al., 2006b). Likewise, complicated mTBI is more likely to have positive neuroimaging findings (Levine et al., 2006; McAllister et al., 2001; Vorst et al., 2007) and significant residuals (Kennedy et al., 2006). If boxing is considered a model for detecting "pre-clinical" or asymptomatic brain injury, recent diffusion tensor imaging studies have demonstrated abnormalities in boxers (Chappell et al., 2006; Zhang et al., 2006b). Thus, animal and human studies support the contention of injury on a continuum, implicating that understanding the variables that relate to severity of injury are

likely very important in understanding neuropsychological sequelae (see Wilde et al., in press; Lewine et al., 2007).

VULNERABILITY OF THE MEDIAL TEMPORAL LOBE AND IN PARTICULAR, THE HIPPOCAMPUS

Elsewhere, I have reviewed research demonstrating that the brain-skull interface in the anterior and middle cranial fossa is a major factor for the vulnerability of these regions in TBI (Bigler, 2007). Potentially the most critical structure injured for neuropsychological sequelae in TBI is the hippocampus and its afferent and efferent connections (Wilde et al., 2007). The Viano et al. (2005b) study demonstrated that the typical deformation of the hippocampus to be 4-6 mm in concussion associated with professional football. Numerous human and animal studies have demonstrated the vulnerability of the hippocampus (and fornix) to injury in TBI (Bigler et al., 2006; Geddes et al., 2003; Royo et al., 2006; Tashlykov et al., 2007; Tasker et al., 2005; Wilde et al., 2006b) and functional neuroimaging studies using SPECT also demonstrate medial temporal lobe hypoperfusion in mTBI (Gowda et al., 2006). Thus, given the location of the hippocampus in the medial temporal lobe and its connection and location to the fornix, these brain regions are key to understanding PPCS neuropsychology, and should be the focus of intense neuropsychological investigation.

LIMITATIONS OF NEUROPSYCHOLOGICAL RESEARCH TO ADVANCE THE FIELD

The Litigation Conundrum: Forensic Implications for Clinical Neuropsychology

From the anatomical and pathophysiological discussions earlier, it is plainly evident that the brain is at least momentarily and transiently injured in concussion but for the majority of those injured persistent sequelae do not occur. Because animal models have demonstrated that lasting negative effects can occur with concussion (see Tashlykov et al., 2007), it is reasonable to assume that PPCS will exist in some individuals. It is in these individuals that neuropsychological research needs to direct its best and most unbiased research efforts. Unfortunately, as pointed out by the World Health Organization's task force on mTBI, poor research designs and the cross-sectional nature of many of the studies on this topic, restrict generalizations of the findings (Carroll et al., 2004a; Carroll et al., 2004b). What can be done to correct short-comings of research in this area?

More than 40 years after Miller (1961) wrote about concussion and "compensation neurosis". Kertesz and Gold (2003), reviewing outcome from concussion make the following statement: "the involvement of insurance claims, litigation, and the expense of rehabilitation makes this area very contentious (p. 629)." Belanger et al. (2005) per-

formed a meta-analysis of 39 studies involving 1463 cases of mTBI assessing clinical neuropsychological test findings. Their findings were similar to what has also been described by Binder et al. (1997), Frencham et al. (2005), and Schretlen & Shapiro (2003), implicating short-term, but not necessarily long-term neuropsychological effects, except for those cases who were in litigation, where either "stable or worsening of cognitive functioning over time (p. 215) was observed." Mooney et al. (2005), in a university based rehabilitation service, examined those with "disappointing recoveries" and observed that "in cases of poor recovery after mTBI where compensation or litigation may be a factor, most of the variance in recovery seems to be explained by depression, pain, and symptom invalidity (p. 975)." With regards to symptom invalidity, Loring et al. (2007) reported 20% of subjects including those with history of head injury who were evaluated in a Universitybased clinical assessment laboratory but who were also in litigation did not pass symptom validity testing (SVT). Plainly, presence of litigation is a major confound in research in mTBI and its presence in research studies has likely obscured the true effects of concussion, including PPCS. Also, whenever analyzing group data, if all subjects with concussion are examined at a particular time period, the effects on individual subjects who may be symptomatic get washed out by the total group effects (Iverson et al., 2006a; Kent, 2007; McHugh et al., 2006; Sterr et al., 2006). This is a very important point, because few studies compare symptomatic versus non-symptomatic subjects who have been concussed and those who do, find those who are symptomatic to have greater neuropsychological impairment (Collie et al., 2006; Iverson et al., 2004; Sterr et al., 2006).

The fact that the litigation process is adversarial and that neuropsychological testimony occurs on both sides of the legal argument, raises the specter of potential bias in what has been written about PPCS depending on the type of forensic work an author may participate in. If one is exclusively retained in legal settings for one side or the other in a legal matter, that could have a bearing on what is studied and reported (Racette et al., 2006). The legal side that retains a clinician or researcher may influence directly or indirectly what is published by that individual (Bigler, 2006). For example, it would be difficult for the individual in private practice whose sole income is derived from their forensic work and consistently retained by the defense to publish on the subtle sequelae of PPCS, including its lasting and enduring adverse effects. Oppositely, but just as likely, the clinician who is exclusively retained by the plaintiff's side is unlikely to publish on the "myth" of PPCS.

Neuropsychological research from countries that do not have the kind of litigation and medical care system that the United States has may provide important information about PPCS, if the proper large scale studies are done. There are cultural differences in the expression of whiplash associated disorders (WAD) (Obelieniene et al., 1999), and the same may be expected in PPCS. Incomplete effort is another major factor contaminating any study looking at long-term

neuropsychological sequelae of concussion (Ross et al., 2006a; Ross et al., 2006b), which represents a topic of its own for review (Iverson & Binder, 2000).

Ecological Validity of the Clinical Neuropsychological Approach

Ecological validity of neuropsychological assessment remains an ever present concern (Chaytor et al., 2006; Moritz et al., 2004; Odhuba et al., 2005; Wood & Liossi, 2006). As an example, the antemortem clinical neuropsychological testing in the concussed patient previously described who met PPCS criteria and who at autopsy had verified pathology of brain injury, was all normal yet this individual had "real-world" difficulty running his business, problems not evident before his injury (Bigler, 2004). Standardized paperand-pencil tests typically conducted in the sterile laboratory may simply not tap the cognitive symptom being experienced by the individual with PPCS. This very point has been made by Collie et al. (2006) in determining which kinds of measurements are most sensitive in detecting problems in those who remain symptomatic after concussion. Obviously, cognitive skills, in particular working memory and executive function, can place much higher demands on neural integrity in the real world than what can be assessed by any current clinical neuropsychological technique in the laboratory.

Assessment in sports concussion has recognized the need to move beyond traditional neuropsychological assessment with the development of more tailored assessment tools in the athlete with concussion (Broglio et al., 2007; Parker et al., 2007). Such assessments are also taking advantage of computerized and virtual assessment techniques as well as the ability to automate the assessment (Cernich et al., 2007; Iverson et al., 2005; Schatz & Putz, 2006; Slobounov et al., 2006). Likewise, various cognitive neuroscience measures either by themselves or combined with functional neuroimaging methods hold great promise for more accurate assessment of the effects of TBI on behavior and cognition (Bergemalm & Lyxell, 2005; Casson et al., 2006; Chan, 2001; Chen et al., 2007; Cicerone et al., 2006; Dockree et al., 2006b; Jantzen et al., 2004; Mendez et al., 2005; O'Keeffe et al., 2007a; O'Keeffe et al., 2007b; Scheibel et al., 2007; Suh et al., 2006). These types of studies applied to PPCS will likely advance the field rather than another round of testing with traditional "clinical" neuropsychological measures (Heitger et al., 2004, 2005, 2006).

Confounding Factors That Must be Considered in the Design of PPCS Studies and the Accurate Determination of Neuropsychological Sequelae

The fact that the eight symptoms of PCS [i.e., (1) becoming fatigued easily, (2) disordered sleep, (3) headache, (4) vertigo or dizziness, (5) irritability, (6) anxiety, depression or

affective lability, (7) changes in personality, and (8) apathy or lack of spontaneity] as outlined by DSM-IV (pp. 704-705) all overlap such that all coexist with a myriad of other medical and psychiatric diagnoses, underscores how complicated the design of the ideal study has to be to truly assess PPCS. For example, Iverson (2006) points out the commonness of misdiagnosing PPCS when the symptoms are really driven by depression and how depression can be misattributed to concussion (Chamelian & Feinstein, 2006; Meares et al., in press). In fact every PPCS symptom can occur independent of a head injury (Iverson et al., 2007). Also, a threshold issue exists where symptoms have to rise beyond a baseline before PPCS can be diagnosed (Chan, 2005). Post-traumatic pain correlates with presence of PPCS (Sheedy et al., 2006); and pain has its own set of correlates, by itself, potentially affecting cognitive performance and emotional status (Alfano, 2006; Karp et al., 2006). None of this even addresses the complexity of WAD, as already mentioned, and WAD pain-related problems (Holm et al., 2006; Johansson, 2006; Zumsteg et al., 2006), nor post-traumatic headaches (Lew et al., 2006; Weiss et al., 1991) which are commonplace in concussion, especially those caused by MVAs.

Not only is the brain concussed, but also other organs such as the eye, inner ear, and soft internal organs (Frater & Haindl, 2003; Keane & Baloh, 1992; Nolle et al., 2004); and injury to these organs can be a source of symptoms. With regards to organs of the head, vertigo, dizziness, tinnitus, and ocular disturbance are commonplace; and they relate to cognitive sequela associated with mTBI (Suh et al., 2006). Presence of any of these symptoms may confound the neuropsychological presentation and sequela of the mTBI patient but are rarely controlled. What is particularly important about pain, regardless of its source, is that pain changes the functioning of the brain, demonstrated by both structural as well as functional imaging (Schweinhardt et al., 2006). Also, the nature and extent of early medication treatment in those who sustain mTBI, may also relate to who develops PPCS (Meares et al., 2006).

Fatigue is a common and persistent problem in PCSS (Stulemeijer et al., 2006; Ziino & Ponsford, 2006), and it too has its own set of neurochemical, neuroimaging, and neuropsychological differences (de Lange et al., 2004; Kozora et al., 2006). The same can be said about the co-occurrence of PTSD in those involved in accidental injury or assault as the source of their concussion (Bryant, 2001; Creamer et al., 2005; McCauley et al., 2001) and the role of stress hormones in the behavioral response to injury (Sojka et al., 2006). PTSD alone has its own unique effect on neuropsychological performance (Vasterling & Bremner, 2006; Vasterling et al., 2006; Veltmeyer et al., 2005). Even for those who do not develop PTSD, being in an accident (Mayou & Bryant, 2002) or an assault (Johansen et al., 2006) or just sustaining a brain injury (Prigatano et al., 2005) is stress producing.

Mooney and colleagues have documented that many with persistent symptoms following concussion meet criteria for

conversion disorder (CD (Mooney & Speed, 2001). However, the neurobiology of CD, including neuroticism, is starting to emerge and it may not be as "functional" as believed (Allet & Allet, 2006; Atmaca et al., 2006; Ghaffar et al., 2006; Schonfeldt-Lecuona et al., 2006; Stonnington et al., 2006; Ward et al., 2003; Wright et al., 2006). Theories and functional neuroimaging studies of CD imply the involvement of limbic regions, inferior frontal and medial temporal lobe structures, the very regions most likely injured in TBI. Is there an increased prevalence of conversion disorder in individuals concussed because these areas are injured? Neuropsychology should be exploring the potential neurobiology of this observation, not merely writing this off as a mere functional manifestation of concussion (Ashman et al., 2006). Recently, Wood (2005) has put forth a diathesisstress model as a beginning attempt to describe these relationships.

It has long been known that pre-morbid factors predispose those with history of neuropsychiatric disorder to be more likely to experience PPCS once concussed (Karzmark et al., 1995; Ponsford, 2005). As such, any study that examines PPCS that does not take into consideration pre-morbid factors likely overlooks important and relevant information that may contribute to the disorder.

It is interesting that only recently has research begun to examine the role of pituitary injury in TBI to functional outcome, even in concussion (Acerini et al., 2006; Kelestimur, 2005; Kelly et al., 2006; Tanriverdi et al., 2007). As shown by the Bayly et al. (2005) and Viano et al. (2005b) studies, the hypothalamic-pituitary axis is particularly vulnerable to physical strain in concussion. Pituitary dysfunction can be associated with many of the same symptoms as seen by PPCS (Casanueva et al., 2006; Powner et al., 2006), yet this has not been systematically investigated in PPCS. This is particularly important because of some pituitary associated physical and neuropsychiatric symptoms are treatable.

Similarly, the basal forebrain resides just anterior to the hypothalamus housing important nuclei and pathways for cholinergic innervation of the brain. The basal forebrain is another region that sustains significant strain effects in biomechanical modeling of concussion and in moderate or greater injury, is consistently damaged (Bigler, 2005; Conner et al., 2005). However, this region has never been systematically examined in PPCS.

The elegant reconstruction of concussion by Viano et al. (2005b) clearly demonstrates that each concussion places unique stress and strain on the brain. Just as clear from this research is that no two concussions are identical in terms of how the brain is impacted. So if one does not take into consideration the impact and physical dynamics of the injury and subject characteristics (including genetics), neuropsychological sequelae could vary widely with regards to the brain regions most likely injured even though all subjects had sustained a "concussion". Unfortunately, for most research on PPCS such information has never been obtained and this has never been systematically investigated other

than in sports concussion. For example, concussion in MVA victims may be different depending on whether it was a front, side or rear impact, whether the car spun, rolled or flipped, etc., the type of car driven, and how and what seat belts were worn, etc. (Elliott et al., 2006). To date this heterogeneity in injury dynamics has simply been overlooked and all such subjects are merely lumped into a single category yet these injury dynamics may make a significant difference in how and where the brain is injured, differences that may be critical in the expression of PPCS.

The prospective design used by the McCrea et al. (2003) study is the proper prototype and standard that should be sought in studying PPCS in non-sports related concussion. To date this has not been done and therefore there are no large-scale, long-term prospective studies of non-sports related concussion that have been conducted. However, the study by Jackson et al. (2007) is a first attempt to accomplish such, where they examined their university-based Trauma I center registry for a single year and identified 97 adult trauma patient survivors from their ICU who had negative CT scan for intracranial hemorrhage, ostensibly eliminating those with obvious severe head injury. Within 12 to 24 months post-discharge, they were able to follow-up with a comprehensive neuropsychological battery of tests on 58 of these subjects and presence of concussion was associated with poorer neuropsychological outcome.

CONCLUSION

From a neuropathological standpoint, this review demonstrates that concussion can lead to structural damage. From the biomechanics of concussion, the vulnerability of the upper brainstem, hypothalamic-pituitary axis, medial temporal lobe and basal forebrain and long-coursing white matter fibers, particularly involving the corpus callosum and fornix are the brain regions most likely to give rise to post-concussive symptoms.

Confusion in the literature on this topic comes from differences in terminology and definitional standards as well as poor research designs where small sample sizes, samples of convenience, selected clinical sub-samples and research that may have an agenda behind it has created serious interpretative problems with regards to the neuropsychology of concussion and its sequelae. Prospective studies of concussion where large trauma centers assess, follow and tract patients with concussion and follow such a cohort prospectively using uniform and more ecologically valid cognitive assessment protocols simply have not been done. In such a group it would be reasonable that additional data could be obtained that would provide more information about the biomechanics of injury and a host of other medical and demographic factors, including attempts to be establish preinjury level of function. In one of the largest reviews of mTBI, the WHO task force that reviewed mTBI literature up to 2004 concluded that mTBI research is "of varying quality and causal inferences are often mistakenly drawn from cross-sectional studies (p. 84," (Carroll et al., 2004a),

see also (Ragnarsson, 2006) The only correction for this gaffe in the neuropsychology of concussion, and potential long-term sequelae of PPCS, will be large, unbiased prospective studies that address the issues raised in this review. The importance of understanding this more accurately and completely is the fact that concussion is reportedly the most common of all neurological injuries and this is also true of the Iraq and Afghanistan war (Das & Moorthi, 2005; Okie, 2005; Warden, 2006; Warden & French, 2005), where unofficial estimates place the numbers in the tens of thousands (Bob Woodruff Reports. February 27, 2007: www.abc-.com), potentially as high as, "1 out of every 10 returning service men and women" [p. 16, American Academy of Neurology News, 20(6), 2007]. Neuropsychology needs to better understand PPCS and this review offers a number of very testable hypotheses for future research.

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EXHIBIT 23

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[Primary Care]



Is There Chronic Brain Damage in Retired NFL Players? Neuroradiology, Neuropsychology, and Neurology Examinations of 45 Retired Players

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Background: Neuropathology and surveys of retired National Football League (NFL) players suggest that chronic brain damage is a frequent result of a career in football. There is limited information on the neurological statuses of living retired players. This study aimed to fill the gap in knowledge by conducting in-depth neurological examinations of 30- to 60-year-old retired NFL players.

Hypothesis: In-depth neurological examinations of 30- to 60-year-old retired players are unlikely to detect objective clinical abnormalities in the majority of subjects.

Study Design: A day-long medical examination was conducted on 45 retired NFL players, including state-of-the-art magnetic resonance imaging (MRI; susceptibility weighted imaging [SWI], diffusion tensor imaging [DTI]), comprehensive neuropsychological and neurological examinations, interviews, blood tests, and APOE (apolipoprotein E) genotyping.

Level of Evidence: Level 3.

Methods: Participants' histories focused on neurological and depression symptoms, exposure to football, and other factors that could affect brain function. The neurological examination included Mini-Mental State Examination (MMSE) evaluation of cognitive function and a comprehensive search for signs of dysarthria, pyramidal system dysfunction, extrapyramidal system dysfunction, and cerebellar dysfunction. The Beck Depression Inventory (BDI) and Patient Health Questionnaire (PHQ) measured depression. Neuropsychological tests included pen-and-paper and ImPACT evaluation of cognitive function. Anatomical examination SWI and DTI MRI searched for brain injuries. The results were statistically analyzed for associations with markers of exposure to football and related factors, such as body mass index (BMI), ethanol use, and APOE4 status.

Results: The retired players' ages averaged 45.6 ± 8.9 years (range, 30-60 years), and they had 6.8 ± 3.2 years (maximum, 14 years) of NFL play. They reported 6.9 ± 6.2 concussions (maximum, 25) in the NFL. The majority of retired players had normal clinical mental status and central nervous system (CNS) neurological examinations. Four players (9%) had microbleeds in brain parenchyma identified in SWI, and 3 (7%) had a large cavum septum pellucidum with brain atrophy. The number of concussions/dings was associated with abnormal results in SWI and DTI. Neuropsychological testing revealed isolated impairments in 11 players (24%), but none had dementia. Nine players (20%) endorsed symptoms of moderate or severe depression on the BDI and/or met criteria for depression on PHQ; however, none had dementia, dysarthria, parkinsonism, or cerebellar dysfunction. The number of football-related concussions was associated with isolated abnormalities on the clinical neurological examination, suggesting CNS dysfunction. The APOE4 allele was present in 38% of the players, a larger number than would be expected in the general male population (23%-26%).

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Conclusion: MRI lesions and neuropsychological impairments were found in some players; however, the majority of retired NFL players had no clinical signs of chronic brain damage.

Clinical Relevance: These results need to be reconciled with the prevailing view that a career in football frequently results in chronic brain damage.

Keywords: concussion; brain injury; neuroradiology; neuropsychology; clinical neurology; chronic traumatic encephalopathy (CTE)

ecent articles have reported an abnormal neuropathology in the brains of deceased football players. 4,22,23,49-51,60,61,72,75 Two surveys of retired National Football League (NFL) players have suggested that depression and cognitive problems occur at increased frequency. 25,26 However, there has only been 1 report of neurological, neuropsychological, and neuroradiological examinations of living, retired NFL players. 31

This stands in contrast to the CTE of boxers. Numerous scientific articles have documented the clinical neurological findings, neuropsychological test results, and neuroradiological findings that characterize CTE in living boxers. ^{11,15,35,45,56,62,70,71} A well-defined neuropathologic pattern of findings for boxers has been reported with correlation to the clinical picture. ¹⁴

The purpose of this study was to fill in this gap in our knowledge by performing clinical neurological, neuropsychological, and neuroradiological examinations on a group of living, retired NFL players. It complements other work. ^{10,12,13,68,69,80} As originally envisioned, the purpose of the study was to determine whether there was clinical evidence of chronic brain damage related to a career in the NFL. As a result of nonscientific factors, recruitment of study subjects stopped part way through the study, and the authors are reporting on a convenience sample of the 45 retired NFL players who were thoroughly examined.

MATERIALS AND METHODS

The methodology for this clinical research was modeled after a similar study of 18 retired and active boxers. ¹¹ The boxers underwent neurological examination, electroencephalography (EEG), brain computed tomography scans, and neuropsychological testing. Most of the boxers (16/18) had definite signs of brain damage, and all had abnormal results on at least 1 neuropsychological test. The conclusion was that brain damage is a frequent result of a career in professional boxing.

With the assistance of the NFL Players Association, recruitment letters were mailed to more than 5000 retired NFL players whose contact information was on file at the union. The letter explained the purpose and nature of this study. Recipients who were interested in participating in the study or who had questions about the study were asked to call the study coordinator at a confidential, dedicated telephone number. Recipients were also informed that they might be called on the telephone by the study coordinator to ask for their participation. The study coordinator randomly selected names from the list and called them on the

telephone to invite their participation. As the study progressed, some of the subjects who went through the study evaluation spontaneously contacted former teammates and other retired NFL or college friends of theirs and suggested that they might also wish to participate. Some of those who were contacted in that manner called the study coordinator and expressed interest in participating. They were accepted into the study if they met the inclusion criteria (see Appendix, Supplement S1; available at http://sph.sagepub.com/content/suppl).

For this study, a more comprehensive magnetic resonance imaging (MRI) evaluation of the brain was used based on state-of-the-art methods under development at Wayne State University. 27-30,37-41,53,73,74.77 Emphasis was also placed on using modern neuropsychological tests, clinical examination, and obtaining a detailed neurological and concussion history. The research methods were subjected to institutional review board review and approval at Wayne State University, including informed consent, methodologies, confidentiality, and statistical analysis. Details regarding the recruitment process and exclusion criteria are available in Supplement S1 (see Appendix).

Each subject underwent all study-related testing during 1 day at the medical center. Written informed consent was obtained from each subject by the study coordinator on the day of testing before any evaluations were performed.

Each subject underwent a comprehensive clinical neurological examination performed by the same experienced neurologist. Details of the neurological examination and history-taking procedures can be found in Supplement S2 (see Appendix, available at http://sph.sagepub.com/content/suppl).

Each subject had blood drawn that was sent to an accredited commercial laboratory for the following tests: complete blood count (CBC), routine chemistries, liver function, thyroid-stimulating hormone (TSH), B12, and folate and Lyme antibodies. A portion of each subject's serum sample was frozen and sent to Duke University Medical Center in North Carolina for APOE (apolipoprotein E) genotyping.

A registered nurse (RN) administered the Patient Health Questionnaire (PHQ) and the Coding Race/Ethnicity in the Columbia University ADRC questionnaire to each subject. The RN also supervised administration of the computerized ImPACT test to each subject.

A board-certified neuropsychologist (PhD) or senior-level neuropsychology PhD candidate (in 42 cases, the neuropsychologist was not affiliated with the NFL or any of its teams; in 3 cases, the neuropsychologist was a team neuropsychologist for an NFL team) administered a battery of

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pen-and-paper neuropsychological tests to each subject. This test battery was put together by a committee of 5 National Academy of Neuropsychology members, 3 of whom were not affiliated with the NFL or its teams. Details regarding the written neuropsychological test administration can be found in Supplement S3 (see Appendix, available at http://sph.sagepub.com/content/suppl).

Each subject was assigned an integer score for each aspect of the testing results. Details of the scoring system can be found in Supplement S4 and Table S1 (see Appendix, available at http://sph.sagepub.com/content/suppl).

Neuroradiology Imaging Protocol

The MRI protocol consisted of baseline T1, T2, T2* gradient echo, and fluid attenuated inversion recovery (FLAIR) sequences, as well as susceptibility weighted imaging (SWI) and diffusion tensor imaging (DTI) sequences. The imaging parameters are given in Table S2 (see Appendix, available at http://sph.sagepub.com/content/suppl). The total data acquisition time lasted approximately 1 to 1.5 hours. The SWI sequence consists of a strongly susceptibility weighted, low bandwidth (80 Hz/pixel) 3D FLASH sequence (TR [repetition time]/TE [echo time] = 50 ms/40 ms, FA = 15°) with first-order flow compensated in all 3 orthogonal directions. ⁷⁸ The SWI sequence included the majority of the cerebral hemispheres and the posterior fossa, with an acquisition time of approximately 7 minutes and 42 seconds. DTI data were collected with 6 gradient directions uniformly spaced on the surface of a b = $1000 \text{ s/mm}^2 \text{ sphere } (TR/TE = 6500 \text{ ms}/100 \text{ ms}, \text{ voxel size} =$ $2 \times 2 \times 3$ mm³, EPI factor = 96, time duration = 7 minutes and 43 seconds).

Postprocessing

Susceptibility weighted imaging data were reviewed by a neuroradiologist and MR scientist, both with more than 30 years' experience, and suspicious hemorrhagic lesions were confirmed by both. The total number and volume of hemorrhagic lesions detected by SWI were analyzed and quantified with our in-house developed software package (Signal Processing for NMR [SPIN]; MRI Institute for Biomedical Research).

DTI Data Processino

A global white matter (WM) fractional anisotropy (FA) mean analysis was performed by using an approach described in previous work⁶ that has been shown to be sensitive to mild traumatic brain injury (TBI). In this approach, each subject's FA map was first spatially normalized to an FA template (mean, 50 normal controls) and then segmented using SPM8 to give gray matter (GM), WM, and cerebrospinal fluid (CSF) masks. A WM-only FA image was then generated to give a global WM FA.

All MRI interpretations were performed by board-certified neuroradiologists. Each subject was then given an integer score for anatomical MRI results and DWI results. The scoring for SWI was as follows: 0 = no microbleeds, 1 = 1 or more microbleeds. Anatomical MRI scoring was as follows: 1 = completely normal;

2 = pituitary microadenoma and/or empty sella; 3 = small cavum septum pellucidum (no cavum vergae, no enlarged ventricles); 4 = large cavum septum pellucidum plus cavum vergae plus enlarged ventricles; 5 = unidentified bright objects (UBOs), cerebral white matter, 3 or fewer; 6 = cortical scar, cerebral; 7 = pituitary macroadenoma; 8 = old small intraparenchymal hemorrhage. Subjects can be assigned more than 1 integer score for anatomical MRI.

Statistics

Descriptive statistics were used to characterize the information and to study correlations and associations among the results. The various demographic and personal history data were correlated to the medical findings using stepwise logistic regression using cumulative, general, or binary logit or linear regression.

RESULTS

The biometric and clinical data on the sample of 45 retired NFL players is given in Tables S3 and S4 (see Appendix, available at http://sph.sagepub.com/content/suppl). The mean age of the retired players was 45.6 ± 8.9 years (range, 30-60 years). The mean number of years in the NFL and NFL training camps was 6.8 ± 3.2 years (range, up to 14 years). The players had 4.2 ± 0.4 years (range, 3.0-5.0 years) of college football, 3.5 ± 0.9 years (range, up to 5 years) of high school, and 2.5 ± 2.3 years (range, up to 9 years) of pre–high school football experience. Their mean height was 75.0 ± 1.8 inches (range, 71-79 inches), and their mean weight was 255 ± 46 lb (range, 178-365 lb). The mean body mass index (BMI) was 31.4 ± 4.8 kg/m² (range, 22.6-42.1 kg/m²).

The players in the sample reported having 6.9 ± 6.2 concussions (range, up to 25) in the NFL. Thirty-four subjects (75.6%) reported that they had sustained 3 or more concussions during their NFL careers. Overall, they reported experiencing 9.0 ± 6.9 concussions (range, up to 25) in all football play. The primary football positions played in the NFL were: 14 linebackers, 9 offensive linemen, 8 defensive linemen, 8 defensive backs, 2 wide receivers, 2 running backs, 1 tight end, and 1 who played both offensive and defensive line. There were no NFL quarterbacks in the sample. Almost all subjects had played on special teams at some point during their NFL careers.

Symptoms

All subjects were asked 9 specific questions relating to cognition and memory. Twenty-three subjects endorsed between 0 and 2 of these symptoms, 11 endorsed between 3 and 5 of these symptoms, and 11 endorsed between 6 and 9 of these symptoms. Every subject was asked 9 specific questions relating to anxiety and/or depression. Nineteen subjects reported 0 or 1 of these symptoms, 14 reported 2 or 3 of these symptoms, and 12 reported 4 to 8 of these symptoms.

Family History

Ten subjects had a family history of Alzheimer disease, dementia, or "senility." Eight subjects had a family history of vol. 6 • no. 5

depression, anxiety, and/or suicidality. Nine subjects had a family history of stroke. Four subjects had a family history of other neurological diseases.

Clinical Neurological Examination

The clinical neurological examination results have been broken down into 3 categories in Table S5 (see Appendix, available at http://sph.sagepub.com/content/suppl): mental status, examination of CNS functions excluding mental status, and examination of peripheral nervous system functions.

Bedside Mental Status

Thirty-eight subjects were normal, 3 subjects could only name 10 or fewer "B" words in 1 minute, 3 subjects could only name 3 or fewer US presidents in reverse order, 1 subject was unable to give the correct meaning of a well-known proverb, and 1 subject had bilateral palmomental reflexes. The range of Mini-Mental State Examination (MMSE) scores was between 25 and 30. For more details, see Supplement S5 (see Appendix, available at http://sph.sagepub.com/content/suppl).

Central Nervous System Examination

Thirty-four subjects were normal, 3 subjects had Babinski signs (2 bilateral and 1 unilateral), 2 subjects had abnormal smell sensation, 2 subjects had mild tremors (sustention and/or intention, not resting), 1 subject had minimal horizontal nystagmus on lateral gaze, 1 subject had diminished pin sensation unilaterally on the chin, and 4 subjects had abnormal dynamic visual acuity testing. None of the subjects had any parkinsonian signs.

Peripheral Nervous System Examination

Twenty-seven subjects were normal, and 18 subjects were abnormal. Seven subjects had signs of lumbar radiculopathy, 4 subjects had signs of cervical radiculopathy, 7 subjects had signs of carpal tunnel syndrome, 6 subjects had signs of ulnar nerve dysfunction, and 3 subjects had signs of diabetic polyneuropathy. Some subjects had more than 1 peripheral nervous system (PNS) abnormality.

APOE Genotyping

Seventeen subjects (37.8%) had at least one allele 4. Two of these had 2 copies of allele 4, while 2 were paired with an allele 2 and 13 were paired with an allele 3. Four subjects had 1 copy of allele 2. Two of these were paired with an allele 4, and the other 2 were paired with an allele 3. Twenty-four subjects had 2 copies of allele 3. Three subjects with at least 1 copy of allele 4 had a family history of Alzheimer disease or dementia. Seven of 28 subjects not carrying an allele 4 had a family history of Alzheimer disease, dementia, or senility. One of the allele 4 carriers had a family history of depression, anxiety, or suicidality, compared with 7 of 28 not carrying that allele who had such a family history. Five of the allele 4 carriers were offensive linemen, 5 were linebackers, 4 were defensive backs, 2 were wide receivers, and 1 was a running back. None were defensive linemen.

Depression Testing

On the Beck Depression Inventory (BDI), 30 subjects scored between 0 and 13 (not depressed), 9 subjects scored between 14 and 19 (mildly depressed), 3 subjects scored between 20 and 28 (moderately depressed), and 3 subjects scored 29 or higher (markedly depressed). Nine subjects fulfilled the criteria for either major depression or other depression on the PHQ. Eight of these 9 subjects also scored 14 or higher on the BDI.

Laboratory Results

There were no major abnormalities. For details, see Supplement S6 (see Appendix, available at http://sph.sagepub.com/content/suppl).

Anatomical MRI

Two cases were found with abnormally enlarged ventricles and thin corpus callosum, which suggests brain atrophy. The brain images can be found in Supplement Figures S1 and S2 (see Appendix, available at http://sph.sagepub.com/content/suppl), which show that both cases had significant atrophy of the brain.

Thirty-four subjects had a cavum septum pellucidum (CSP) on their MRIs. Three of these were large and associated with a cavum vergae, and 31 were small. There were no other anatomical MRI findings that occurred with any significant frequency. There were 3 subjects with large CSPs: One (patient 5) played 4 years in the NFL, 4 years in college, 4 years in high school, and 6 years of pre-high school football. He reported 4 total concussions (2 in the NFL) and 10 dings (all in the NFL, see supplement S2 for definition of "ding"; Appendix). The second player (patient 10) played 13 years in the NFL, 4 years in college, 4 years in high school, and 4 years in pre-high school. He reported 25 concussions (all in the NFL) and 30 total dings (25 in the NFL). The third player (patient 36) played 1 year in the NFL (went to 2 NFL training camps, thus would have been considered a "control" subject under the original study criteria), 5 years in college, 2 years in high school, and 1 year before high school. He reported 5 concussions (0 in the NFL) and 6 dings (0 in the NFL).

One subject had a pituitary macroadenoma. Two subjects had developmental venous abnormalities. There were no extra-axial collections and minimal unidentified bright objects.

Neuroradiology/SWI

Susceptibility weighted imaging detected 4 cases with microbleeds and 1 case (patient 30) with abnormal vascular malformation (possible telangiectasia). Table 1 shows the SWI lesion number and total volume (mm³) for the 4 cases in the study.

One subject was 57 years old (patient 10), played 13 years in the NFL, had more than 20 NFL concussions, normal CNS examination, MMSE score of 27, BDI 4, carried the APOE4 allele (E3/E4), and has a history of high cholesterol. Figure 1 shows the microbleed. The second subject was 30 years old (patient 16), played 5 years in the NFL, had 5 NFL concussions, had a

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Table 1. Detailed data on 4 players

	Case ID					
	10	16	22	31		
Age, y	57	30	32	52		
Years of NFL Play	13	5	8	2		
No. of Concussions	20+	5	8	0		
Bleed Location	CR	FP GM	CR	BS		
Volume, mm ³	21	434	62	57		
T1	Enlarged ventricles	-	-	-		
CSP/CV	+/+	+/-	+/-	+/-		
MMSE	27	28	26	29		
BDI	4	3	17	8		
APOE4 Allele	+	+	-	-		
Prehistory	None	Severe TBI*	None	None		
Cardiovascular Record	High cholesterol	Hypertension	None	Hypertension		

APOE, apolipoprotein E; BDI, Beck Depression Inventory; BS, brain stem; CR, corona radiata; CSP/CV, cavum septi pellucidi/cavum vargae; CVI, cavum veli interpositi; FP GM, left frontal gray matter; MMSE, Mini-Mental State Examination; TBI, traumatic brain injury. All central nervous system examinations were normal.

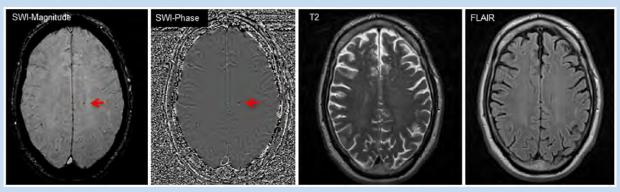


Figure 1. Microbleed in a 57-year-old player (patient 10). Both SWI magnitude and phase images detect an isolated microbleed at the subcortical gray matter/white matter (GM/WM) junction, while conventional FLAIR and T2-weighted images at the same level fail to visualize the microbleed. Red arrows point to a hemorrhagic lesion, which is not shown on the T2 and FLAIR images. FLAIR, fluid attenuated inversion recovery; SWI, susceptibility weighted imaging.

normal CNS examination, normal MMSE and BDI, had the APOE4 allele (E3/E4), had a serious head injury with possible skull fracture when he was 9 years old, and has a history of hypertension. Figure S3 in the supplemental information shows the microbleed (see Appendix, available at http://sph.sagepub.com/content/suppl). The third subject (patient 22) was 32 years old, played 8 years in the NFL, had 8 NFL concussions, normal CNS examination, BDI 17, MMSE 26, no history of medical illnesses, and did not carry the APOE4 allele (E3/E3). Figure 2

shows the microbleed. The fourth player (patient 31) was 52 years old, played only 2 years in the NFL as a backup, had 0 concussions in the NFL (or for that matter, at any level of football), completely normal clinical examinations, did not carry the APOE4 allele (E3/E3), and has a history of hypertension and treated CLL. He is one of the subjects designated as having limited NFL exposure in our article. Figure S4 in the supplemental information shows the microbleed (see Appendix, available at http://sph.sagepub.com/content/suppl).

^{*}Left parietal skull surgery with thick dura under it.

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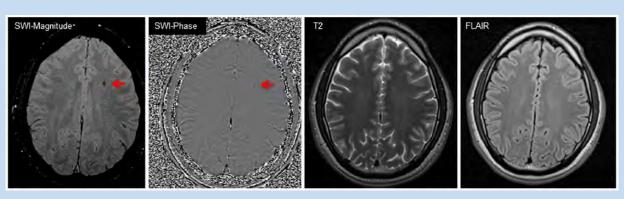


Figure 2. Microbleed in a 32-year-old player (patient 22). Both SWI magnitude and phase images demonstrate a microbleed (arrows) in left superior corona radiata, which conventional MRI (FLAIR and T2-weighted) did not detect. FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging.

Diffusion Tensor Imaging Findings

The average DTI FA mean, peak, and mean/peak for the sample's whole-brain global white matter is given in Table S5 in the supplement (see Appendix).

Neuropsychology

None of the players had dementia (defined as impairments on 2 or more spheres of cognition that interfere with activities of daily living). Twenty-eight players (62%) had no impairments (score 0 or 1). Eleven (24%) players had impairments on 1 or 2 of the subtests with normal Test of Memory Malingering (TOMM) and verbal IQ (score 2 or 3). Six players (13%) had borderline or impaired performance on 1 or more subtests, but the results are confounded by verbal IQ less than 80 or lack of effort as determined by the TOMM results. The overall results of the written neuropsychological test battery are provided in Tables S4 and S5 in the supplement (see Appendix).

Computerized neuropsychological testing was scored by a computer, and the results generated included raw scores and composite scores on various aspects of memory/cognitive function. In the absence of a control group, we used the composite test scores for statistical analysis.

Statistical Analysis

In the absence of a control group, we performed a set of statistical analyses aimed at determining if there were associations between a representative group of "epidemiological" variables (x) that serve as markers of football exposure, head injury exposure, and non-football- or head injury-related variables such as ethanol use, hereditary factors, and BMI and the results of the diagnostic tests (y) performed on the subjects. The football-related variables were chosen as markers of total football exposure, football exposure before college, football exposure at the college level, and football exposure in the NFL. Statistical analyses of the association

between these variables and the results of MRI, neuropsychological testing, clinical neurological testing including mental status, and depression testing can help to elucidate the role of these exposures in causing any abnormalities or other findings detected by the clinical tests.

There was no statistical association between the anatomical MRI findings and any football exposure–related variables. There was a correlation between the presence of findings on SWI MRI and family history of neurological disease, employment status, and number of dings in football at all levels ($\chi^2 = 2.75$, df = 6, $Pr > \chi^2 = 0.8399$ for the Hosmer and Lemeshow goodness of fit). This indicates that the presence of findings on SWI MRI might be because of both genetic and environmental (ie, number of dings) factors. SWI microbleeds were related to the number of dings in football ($\chi^2 = 0.276$, df = 4, $Pr > \chi^2 = 0.9913$ for the Hosmer and Lemeshow goodness of fit). None of the other "x" variables related to playing in the NFL correlated with the presence of microbleeds on SWI MRI.

Peak FA was negatively associated with presence of the APOE4 allele, participation in other contact sports besides football in high school and/or college, and with ever having been "dinged" in football at any level. Peak FA was positively associated with 1 marker of inappropriate ethanol use, employment status, and number of years of participation in pre–high school football. Mean FA was negatively associated with the number of concussions sustained in the NFL.

Depression scores were not statistically associated with any of the markers of football exposure. There was no statistical association between written neuropsychological test results and any football exposure–related variables. Written neuropsychological test results were statistically associated with BMI and ethanol usage.

In regard to computerized neuropsychological subtest results, there were statistical associations with having played a line position (visual memory subtest), years of pre-NFL football play asson et al Sep • Oct 2014

(verbal memory and motor subtests), the number of "dings" sustained in NFL play (motor subtest), BMI (visual memory), and ethanol usage (multiple subtests). Additional discussion of statistical associations is provided in Supplement S7 and Table S6 (see Appendix, available at http://sph.sagepub.com/content/suppl).

DISCUSSION

This report provides findings of comprehensive neurological, neuropsychological, and neuroradiological evaluations of 45 retired NFL players between the ages of 30 and 60 years. Up until now, there have been 3 mail/telephone surveys of retired NFL players, a number of neuropathological case reports, and 1 clinical evaluation of older retired NFL players in the medical literature. 4,22,23,25,26,31,49-51,60,61,75 There are a number of inherent methodological weaknesses in mail/telephone surveys that cast doubt on their validity and reliability. One major limitation of these surveys is the absence of any objectively verified reports of clinical, neuropsychological, or neuroradiological examinations by physicians on any of the survey respondents. The neuropathological cases that have been reported in the scientific literature have not included detailed reports of clinical, neuropsychological, or neuroradiological findings by physicians on the subjects prior to their demise. 4,22,23,49-51,60,61,75 The medical community is thus confronted by a neuropathological picture without clinical correlation and a dearth of detailed clinical reports of neurological, neuropathological, or neuroradiological findings in living, retired NFL players. The present report is intended to fill in this gap in our knowledge.

The absence of clinical evidence of dementia, dysarthria, parkinsonism, or cerebellar dysfunction in the retired players stands in stark contrast to boxers, who often showed signs of dysarthria, dementia, parkinsonism, pyramidal tract dysfunction, and/or cerebellar dysfunction. ^{11,13,15,35,45,54,62,70,71} There was a statistical association between the presence of abnormalities on the clinical CNS examination and the total number of football concussions sustained at all levels of football. This suggests that mild clinical abnormalities may be the result of sustaining a relatively greater number of football concussions at all levels of play. Whether this is related to CTE is not demonstrated by these data. For example, Roberts⁷⁰ specifically excluded the presence of isolated abnormalities, such as an isolated Babinski sign, as evidence of CTE.

Many more subjects had clinical evidence of PNS dysfunction than CNS dysfunction on clinical examination. The signs of diabetic polyneuropathy found in 3 subjects cannot be attributed to the effects of football-related trauma, but the lumbar and cervical radiculopathies and the ulnar and median nerve compressions found in the subjects most likely are of traumatic origin.

The clinical mental status evaluation did not reveal any subjects with dementia. Among college graduates in the general population, MMSE scores of 24 or lower indicate dementia, and

the lowest score among the study subjects was 25 (subject 25). If one uses a clinical definition of dementia being characterized by disorientation, confusion, and memory loss, there were no study subjects who met these criteria either. If one defines dementia as impairments in multiple spheres of cognitive and memory functions that adversely affect daily activities, there were no study subjects who met these criteria either. There was a statistical association between the presence of abnormalities on clinical mental status testing and the number of years of college football played. This suggests that pre-NFL football exposure might result in mild mental status abnormalities years later.

Depression

Using the BDI criteria, the 15 subjects (33%) with any severity of depression is higher than the reported prevalence of depression in the general population (15%-20%). The 6 subjects with moderate or severe depression (13.3%) are more in line with the overall population numbers. Nine players (20%) met the PHQ criteria for depression, which is in line with the general population prevalence. The evidence in this study does not support the contention that a career in the NFL is causally related to later-life depression. For further discussion, see Supplement S8 (see Appendix, available at http://sph.sagepub.com/content/suppl).

APOE Genotyping

It has been suggested that people who carry at least 1 copy of the E4 allele are at increased risk of developing Alzheimer disease as a result of head trauma. 46,79 It has also been suggested that those carriers have poorer outcomes following head trauma than non–E4 carriers. 11,36,76,79 One study found that the E4 allele is a risk factor for chronic brain dysfunction in boxers. Another study reported that older professional football players (still active in the sport), who were E4 carriers, performed poorer on a battery of cognitive tests than those who did not carry the E4 allele. It is well known that people who carry the E4 allele have an increased risk of developing Alzheimer disease and an earlier age of onset than noncarriers. Some studies indicate that the E4 allele enhances brain tau deposition. 56,79 All of these factors suggest that there might be a link between the E4 allele and chronic CNS dysfunction in retired NFL players.

In all, 37.7% of the study cohort carried at least 1 copy of the E4 allele. This is higher than the 23.2% to 25.6% of men in the general population who are E4 carriers. ^{17,52,79} This is also higher than the 26.4% of the 53 active NFL players who carried the E4 allele in another study. ⁴² One might hypothesize that the APOE4 allele could be associated with athletic prowess and/or improved physical performance. Some studies have demonstrated an effect of APOE allele status on serum lipid responses to exercise and other physical activities. ^{16,43,59} It is also possible that the APOE gene could be linked to another gene that affects physical performance. These possibilities deserve further investigation.

The absence of a statistical association of the APOE4 genotype with any anatomical MRI, clinical neurologic, depression, or

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neuropsychological test results in this sample raises doubts about the possibility that APOE genotype has a clinical expression in retired NFL players 60 years and younger. The statistical association of the APOE4 genotype with FA peak on DTI is consistent with a recent report on the effects of APOE on FA in healthy non–football player volunteers.⁸³

Neuroradiology

Most of the effects of mild TBI, including sports concussion, have been reported to be occult to clinical neuroimaging, including computed tomography and conventional MRI. However, a handful of techniques are sensitive to the subtle changes of the brain after concussion, ^{5,41} including SWI⁴¹ and DTI. ^{2,6,41,57,85} For further details on neuroradiology techniques, see Supplement S9 (see Appendix, available at http://sph. sagepub.com/content/suppl).

Microbleeds

In this study, none of the 4 subjects with microbleeds belonged to the "control" or limited NFL exposure group (see Table 1). One subject had sustained a significant TBI and skull fracture before playing in the NFL. After brain injury, hemorrhagic lesions may undergo a series of temporal evolutions, and macrophage cells may leave hemosiderin in the bleed site. ⁴¹ The hemosiderin may stay in the brain for a long time as evidence of previous injuries. Consequently, the microbleed in this case may be attributed to a previous severe brain injury.

The microbleeds in the remaining 3 cases are likely related to head trauma occurring in football at some level. SWI-detected microbleeds can also be related to amyloid angiopathy and/or hypertension, 3.27,37 but in subjects younger than 60 years, it is more likely that they are etiologically related to head trauma. In several other studies covering hundreds of patients, including mild cognitive impairment and normal controls, microbleeds were rarely found. It is not yet known whether the 9% frequency of microbleeds is higher than what might appear in an agematched normal population; it is unusual to have more than 1 microbleed in a sample our size. Statistical analysis determined an association between total number of dings reported at all levels of football and the presence of microbleeds on SWI, adding further support to the suggestion that head trauma is related to SWI microbleeds in the study subjects.

Magnetic Resonance Diffusion Tensor Imaging

The association between number of years of pre-high school and high school football and FA findings suggests that head injury occurring before the age of 18 years may result in DTI abnormalities that can still be detected many years later. This is consistent with evidence from some other studies suggesting that younger brains are more susceptible to the deleterious effects of head trauma than mature brains. ^{18,44,63-67} On the other hand, it has also been suggested that younger brains may be more tolerant to traumatic biomechanical forces than adult brains. ⁴⁷

The association between number of NFL concussions and the subject's mean FA suggests that concussions occurring at the

NFL level may result in DTI abnormalities that are detectable after NFL retirement. DTI could detect "microstructural" lesions that account for a patient's neurocognitive symptoms but are invisible on structural MRL ^{38,57} The fact that the number of NFL concussions is not correlated with neuropsychological test results raises the possibility that NFL concussions may not result in changes in FA that can be related to clinical or neurocognitive abnormalities. Whether these DTI abnormalities correlate with tau deposition in the brain or other pathological indicators of "CTE" remains a question.

The association between measures of excessive/inappropriate ethanol use and FA results indicates that environmental factors other than trauma can affect FA or that brain-injured subjects could be predisposed to excessive ethanol use or more susceptible to the effects of ethanol. The correlation between presence of the APOE4 allele and FA findings suggests that genetic factors contribute to the amount of anisotropy in the brain. Recent literature suggests that concussion and APOE4 allele are risk factors for neural behavioral impairment. Other studies have demonstrated that axonal injury is a progressive process instead of a single event. This suggests that sports concussion makes those individuals with APOE4 allele genotype more susceptible to WM injury.

Anatomical MRI

Three subjects had large CSPs on MRI. Large CSPs have been radiologically and neuropathologically associated with CTE in boxers. Interestingly, there was no correlation between the presence of a large CSP and any of the "x" factors related to exposure to football and/or head trauma. The prevalence of large CSPs in this group of retired NFL players (6.6%) is much lower than the prevalence (20%) in prior CAT scan studies of retired boxers. 11,71 This is another important difference between the brains of retired football players and retired boxers. Small CSPs have not been associated with CTE in boxers. The absence of a correlation between a small CSP and any of the "x" factors in this study suggests that football-related head trauma is also not associated with small CSPs. A small CSP in 31 of 42 (74%) MRIs (excluding the 3 MRIs with a large CSP) at first glance seems to be higher than what is seen in MRIs of the general population. However, review of the literature reveals that small CSPs have been seen in up to 76% of healthy subjects on 1.5-T MRIs, as were used in this study. 20,48 The radiologists interpreting the MRIs in the present study paid special attention to the septum region because of the known association between septal abnormalities and CTE of boxers. 11,14,54,71 It is possible that paying special attention to the septal region on all MRIs (not only those of football players) may result in a higher incidence of small CSPs being reported in MRIs of the general population in clinical practice.

Written Neuropsychological Testing

None of the subjects had dementia using criteria defined as impairments in 2 or more modalities of cognition/memory (verbal and visual memory, executive functions, motor speed,

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sustained attention/working memory) along with impairments in functions of daily living. Eleven players (24%) had isolated impairments on 1 or 2 subtests not rising to the level of dementia. Three of these 11 had depression (score 2 or 3 on combined depression score). It is known that depression can impair neuropsychological test performance. Nevertheless, the incidence of isolated impairments seems higher than would be expected in the general population younger than 60 years. It is difficult to be certain how this compares with the general male population in the absence of a control group and validated data on the incidence of similar impairments in a general population of similar-aged males.

Statistical analysis suggests that impaired performance on written neuropsychological test results after retirement from the sport and before the age of 60 years is related to non-football factors. The association of impairments on written neuropsychological tests with BMI is not surprising given the evidence in the medical literature linking midlife obesity with cognitive impairment or dementia. 1,19,84 The association of impairments on written neuropsychological testing with ethanol use is also not surprising as it is well known that excessive ethanol use can impair cognition. These results should raise a cautionary red flag to those who would ascribe all findings of cognitive and memory dysfunction in retired NFL players to the effects of football-related head trauma.

Computerized Neuropsychological Testing

In the absence of any association with any football-related factors, the associations between visual memory composite score and those who had played line positions and with higher BMI points more toward an effect of midlife obesity on cognition rather than a football-related etiology. The associations between verbal memory and motor composite scores and years of football play in pre-high school and college suggest that exposure to football before the NFL may impair these cognitive functions later in life. The association between motor scores and the number of NFL "dings" suggests that NFL exposure might impair motor functions later in life. In view of the much higher prevalence of signs of PNS than CNS dysfunction in the study cohort, it is unclear what roles PNS and CNS impairments may play in these motor composite test results. In summary, computerized neuropsychological test scores were related to non-football-, non-head injury-related variables, pre-NFL football exposure, and in regard to motor scores only, the number of dings in the NFL.

Playing football at the pre-NFL level was associated with mild abnormalities on some subtest composites on computerized neuropsychological testing and FA findings on DTI MRI. Playing football in the NFL was associated with FA findings on DTI MRI and abnormalities only on the motor subtest composite of the computerized neuropsychological test battery. Length of NFL career was not associated with any abnormal findings on any part of the diagnostic test battery. In fact, none of the variables used as markers of exposure to football and football head injury were associated with abnormal findings on the great majority of

the diagnostic tests that were performed. Non-football-related head trauma was associated with DTI MRI FA findings and abnormalities on some subtest composites of the computerized neuropsychological test battery, indicating that the effects of non-football-related head trauma must be considered when evaluating the neurological status of retired NFL players. Non-head trauma-related variables such as BMI, inappropriate/excessive ethanol use, hereditary factors, and social factors were associated with at least as many, and perhaps more, abnormal or poorer performances on various parts of the entire test battery than were head trauma- and football-related factors. Others⁹ have pointed out the influence of non-head trauma-related factors on neuropsychological test results. They reported poorer test results with obstructive sleep apnea and consequent hypoxemia, which may be a factor in football linemen.

Is There Chronic Brain Damage?

Some have claimed that there is an "epidemic" of chronic brain injury due to the cumulative effects of head impacts in NFL players. $^{4,22,23,49-51,60,61,72,75}$ They have suggested that chronic brain damage is a frequent occurrence in retired NFL players. The MRI scans in this study revealed probable signs of chronic brain injury in 13% (n = 6) of the players and an association between FA and football exposure. However, FA was also associated with non-football factors such as heredity (APOE status), and 87% (n = 39) of the players did not have MRI findings suggesting chronic brain injury. Eleven players (24.4%) had isolated impairments on written neuropsychological testing, which possibly are related to prior brain injuries, but the presence of these impairments was only statistically associated with non-football head injury factors such as BMI and ethanol overuse and not with any measures of football head injury exposure.

Computerized neuropsychological testing results were statistically associated with numerous factors, including both non-football and football exposures. The prevalence of depression in the cohort is similar to that of the general population.

Comprehensive neurological examinations revealed a few isolated signs of CNS dysfunction (eg, Babinski signs), but no players had dementia, dysarthria, parkinsonism, or cerebellar dysfunction. In his classic book on the subject of brain damage in boxers, Roberts⁷⁰ excluded using isolated findings such as Babinski signs alone in diagnosing chronic brain damage.

Is the Study Cohort Representative of All NFL Retired Players?

Whether or not the study cohort is representative of the entire group of retired NFL athletes plays a major role in how these findings are interpreted. If the study group is representative, then there is not a clinical epidemic of objective neurological dysfunction in living, retired NFL players. Furthermore, the neuropathological picture that has been reported has few clinical correlates. NFL players have a significant genetic susceptibility to Alzheimer type pathology and tau pathology by dint of their increased frequency of APOE4 genotypes

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compared with the general population and their high frequency of reported family history of Alzheimer disease, dementia, and "senility." ^{56,79}

If the study group is not representative, then one needs to ask how it may differ from the entire group of retired NFL players. Have the members of the study group been exposed to more or less NFL football or football at other levels than the overall population of retired NFL players? Do the football positions played by the study subjects reflect those played by the entire population of retired players, and, if not, are the positions played by the study group subjects representative of the NFL positions more or less at risk of sustaining concussions? Are the numbers of concussions reported by the study subjects more or less than those reported by the entire group of retired NFL players? Are the members of the study group of similar ages as the entire population of retired NFL players? Did the members of the study cohort report symptoms of cognitive/memory dysfunction and depression/anxiety at similar, higher, or lower rates than the entire group of retired NFL players? Are the medical, social, and family histories reported by the study subjects representative of those of the entire population of retired NFL players?

The evidence suggests that the study cohort is representative of the entire group of retired NFL players in some respects, and when not representative, consists of subjects with an increased exposure to NFL football and an increased incidence of cognitive/memory and depression/anxiety symptoms compared with the entire group of retired NFL players. Additional discussion is provided in Supplement S11 (see Appendix, available at http://sph.sagepub.com/content/suppl).

Limitations

The authors acknowledge many limitations of the study:

- 1. Control populations. This study was stopped for nonscientific reasons, limiting the number of available age-matched controls. Ideally, it should have at least 2 groups of controls: 1 group with limited duration of NFL exposure and 1 group of normal and healthy controls. They would be the ideal populations to contrast with the retired NFL players to answer the questions of (1) how an NFL career affects an individual's neurocognitive and imaging profile and (2) how playing football itself affects an individual's neurocognitive and imaging profile. This is particularly true for DTI analysis.
- 2. DTI analytical approaches. A global histogram approach, which is used in this study, has been reported as being sensitive to brain injury by 2 groups concurrently. However, the data sets of both studies are more populated with moderate to severe TBI patients instead of patients with mild TBI. Given the subtle nature of possible concussion, a regional or voxel-based instead of global analysis approach could be more sensitive to microstructural changes of the brain after mild TBI. 57,58
- Timing point of MR scan after injury. Studies reported that metabolic levels might be normalized in the chronic stage

- after brain injury.^{32,33} Given the nature of this study design, the subjects are post–playing stage of life, when MRI data may not be sensitive.
- 4. Magnetic field strength. The imaging community is migrating to 3-T magnets from the 1.5-Tesla platform used in this study. The doubled signal to noise ratio of 3-T over 1.5-T magnets provides greater potential to detect subtle changes of the brain, including possible microbleeds, white matter injury, or abnormal metabolic levels.
- 5. MRI spectroscopy was intended to be a part of the MRI study performed on each subject. Due to technical difficulties, adequate spectroscopy could only be obtained on 10 subjects. Because of this small number, spectroscopy results are not included in this report.

CONCLUSION

The present study indicates that MRI detects evidence of probable chronic brain injury related to football in up to 13% of the retired players and neuropsychological testing detects evidence of isolated cognitive impairments not rising to the level of dementia and related to multiple factors, not only football/head trauma, in 24.4% of the retired players. There is no clear evidence of chronic brain damage on depression testing or neurological examination. These results need to be reconciled with the prevailing view that a career in football frequently results in chronic brain damage.

A recent report of autopsy results indicates that 34 of 35 retired professional football players' brains had evidence of "CTE" with a specific pattern of tau pathology, which correlated with a myriad of clinical symptoms ascertained by postmortem interviews with family members and some reviews of medical records. ⁵¹ There is clearly a large disconnect between that report and the clinical, neuropsychological, and neuroradiological findings in the 45 living, retired NFL players detailed here. For further details, see Supplement S10 (see Appendix, available at http://sph.sagepub.com/content/suppl).

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Cerebral microbleeds: a new dilemma in stroke medicine

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DECLARATIONS

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There are no competing interests to declare.

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The manuscript did not require clinical or research ethical approval.

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DJW

Contributorship

PK and AC were responsible for manuscript production and preliminary research. DJW has overseen the entire project with primary input into manuscript formulation, editing and methodology.

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Summary

Cerebral microbleeds (CMBs) are an increasingly common neuroimaging finding in the context of ageing, cerebrovascular disease and dementia, with potentially important clinical relevance. Perhaps the most pressing clinical question is whether CMBs are associated with a clinically important increase in the risk of intracerebral haemorrhage (ICH), the most feared complication in patients treated with thrombolytic or antithrombotic (antiplatelet and anticoagulant) drugs. This review will summarize the evidence available regarding CMBs as an indicator of future ICH risk in stroke medicine clinical practice.

Introduction

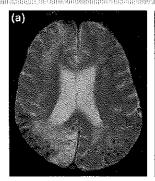
In the mid-1990s reports began to appear of small haemorrhagic lesions on magnetic resonance imaging (MRI) studies. Scharf et al.1 described black dots of signal loss on T2-weighted MRI in patients with spontaneous intracerebral haemorrhage (ICH) and termed these 'haemorrhagic lacunes'. Subsequent studies using T2*-weighted gradient-echo (T2*-GRE) MRI - a technique with greater sensitivity to the signal loss from magnetic 'susceptibility' effects of blood breakdown products - detected small round black dots which have become known as 'cerebral microbleeds' (CMBs).² Because CMBs reflect small areas of haemorrhage, and are common in both ischaemic stroke and ICH,3 they have caused concern regarding the risk of future ICH, especially in patients receiving antithrombotic therapy. Although randomized controlled prospective data are lacking, observational data suggest that CMBs are indeed related to an increased future stroke risk, particularly for ICH. Here, we review the available evidence with reference to common clinical scenarios including those where the optimum management may be uncertain.

Pathology, detection and definition of CMBs

Before considering their clinical significance, it is necessary to briefly discuss aspects of CMB pathology, detection and classification. CMBs are small perivascular haemosiderin-deposits (usually within macrophages) in the brain, generally associated with local vessel wall damage.4 Histopathological analyses of the brains of patients with spontaneous ICH or Alzheimer's disease have shown that CMBs are located in proximity to vessels affected by two types of sporadic small vessel disease: (a) hypertensive arteriopathy and (b) cerebral amyloid angiopathy (CAA).⁵ CMBs are found throughout the brain, including cortical grey and white matter, the basal ganglia and brainstem (Figure 1). A large number of cross-sectional studies have confirmed important risk factors and associations for CMBs,

Figure 1

(a) A T2*-weighted gradient-echo (T2*-GRE) magnetic resonance imaging (MRI) scan of a patient with cognitive decline, showing multiple strictly lobar cerebral microbleeds (CMBs) meeting the Boston criteria for probable cerebral amyloid angiopathy. Note the posterior/occipital distribution of CMBs, characteristic of amyloid angiopathy. (b) T2*-GRE MRI of a patient with a history of long-standing hypertension: CMBs are predominantly located in deep brain structures including the basal ganglia and thalami, consistent with hypertensive angiopathy (including arteriolosclerosis and fibrohyalinosis). CMBs are also visible in lobar brain regions





including age, hypertension, history of stroke (both ischaemic and haemorrhagic) and neuroimaging markers of small vessel disease including white matter changes and lacunar infarcts.6, There is increasing (albeit largely indirect) evidence that the distribution of CMBs reflects the underlying type of microangiopathy (Figure 1). Strictly lobar CMBs are considered likely to be due to CAA, because of their association with known risk factors for CAA including apolipoprotein E e4 genotype.8 Furthermore, an in vivo positron emission tomography amyloid-β imaging study using the ligand Pittsburgh compound B, found that CMBs in patients with CAA corresponded to local regions of high amyloid- β concentration.9 By contrast, deep CMBs are considered most likely to be due to hypertensive arteriopathy because of their associations with hypertension and other imaging manifestations of hypertensive small vessel disease. 10 In clinical practice these arteriopathies (CAA and hypertensionrelated) are frequently likely to coexist and interact. Diagnostic criteria for CAA have been developed (the 'Boston criteria') (Table 1) with the aim of diagnosing CAA in vivo without recourse to tissue biopsy. These criteria include the presence of strictly

Table 1 Boston criteria for diagnosis of CAA-related haemorrhage

1. Definite CAA

Full postmortem examination demonstrating:

- Lobar, cortical or corticosubcortical haemorrhage
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion
- Probable CAA with supporting pathology Clinical data and pathological tissue (evacuated haematoma or cortical biopsy) demonstrating:
 - Lobar, cortical or corticosubcortical haemorrhage
 - Some degree of CAA in specimen
 - · Absence of other diagnostic lesion
- 3. Probable CAA

Clinical data and MRI or CT demonstrating:

- Multiple haemorrhages restricted to lobar, cortical or corticosubcortical regions (cerebellar haemorrhage allowed)
- Age ≥ 55 years
- Absence of other cause of haemorrhage
- 4. Possible CAA

Clinical data and MRI or CT demonstrating:

- Single lobar, cortical or corticosubcortical haemorrhage
- Age ≥ 55 years
- · Absence of other cause of haemorrhage

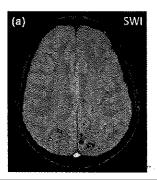
Criteria established by the Boston Cerebrall
Amyloid Angiopathy Group: Steven M Greenberg
MD PhD, Daniel S Kanter MD, Carlos S Kase
MD and Michael S Pessin MD. See Ref. 11
CAA, cerebral amyloid angiopathy;
MRI, magnetic resonance imaging; CT, computed tomography

lobar ICH, including CMBs, and have been shown to have very high specificity. However, the sensitivity of these criteria may be lower, and some patients with a mixed deep and lobar distribution of CMBs, although not fulfilling the Boston criteria, are likely to harbour some degree of CAA. New biomarkers for CAA may help improve the sensitivity of these diagnostic criteria without sacrificing their specificity.

The radiological detection of CMBs is reliant on the paramagnetic property of haemosiderin which disrupts the local magnetic field, causing

Figure 2

(a) Susceptibility-weighted imaging (SWI) is currently the most sensitive means for the detection of cerebral microbleeds (CMBs). Although SWI can detect significantly more CMBs compared with conventional T2*-weighted gradient-recalled echo (T2*-GRE) magnetic resonance imaging, whether it has 'added value' in clinical practice is still under investigation





'inhomogeneities' and focal signal loss (known as 'susceptibility effect') on appropriate MRI sequences including T2*-GRE.¹² Newer MRI techniques to detect CMBs include susceptibilityweighted imaging and its variants, which greatly increases the sensitivity of CMB detection (Figure 2) by combining both the magnitude and phase images to increase susceptibility-related tissue contrast.13 Detection of CMB is influenced by a variety of sequence parameters including the echo time (TE), field strength and slice thickness.14 Moreover, most current methods of defining CMBs rely on manual visual rating of scans, leading to substantial variations in agreement between observers. In an effort to improve agreement about CMB presence, number and location, two rating scales have been developed and validated for use in classifying CMB; The Microbleed Anatomical Rating Scale (MARS)15 and the Brain Observer Microbleed Scale (BOMBS). 16 The MARS rating form (Figure 3) shows the conventional anatomical definition of deep, lobar and infratentorial regions. Lobar regions include cortical and superficial subcortical white matter regions (including subcortical U fibres). Deep regions include the basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep and periventricular white matter. Infratentorial regions include the brainstem and cerebellum. Both of these scales are validated for inter-observer agreement; the main difference is that MARS allows for the categorization of CMB distribution in different brain lobes. It is important to note that there are a number of radiological 'mimics' of CMBs including vascular flow voids, susceptibility artefacts from surrounding tissue (air, bone), cavernous malformations, haemorrhagic transformation of ischaemic areas, diffuse axonal injury and occasional haemorrhagic cerebral metastases.⁴ Recent consensus criteria for the diagnosis of CMBs are summarized in Table 2.

Clinical significance of CMBs for antithrombotic drug treatments

How could CMBs affect the risk of ICH on antithrombotic drugs?

Because CMBs are a radiological marker of previous small areas of bleeding from abnormal cerebral small vessels, a key question is whether they are predictive of an increased risk of ICH in individuals treated with antithrombotic medications. It is generally assumed that most CMBs are clinically 'silent' and self-limiting because of haemostatic mechanisms and surrounding tissues. However, it is hypothesized that leakage of blood from an arteriolar rupture may on some occasions not be stemmed, resulting in potentially serious symptomatic ICH. Antithrombotic agents (antiplatelet or anticoagulant drugs) may, by impairing platelet function or the endogenous coagulation cascade, increase the likelihood of ICH resulting from a CMB. For CMBs to have clinical relevance for antithrombotic-related ICH they must first be common in the populations likely to be exposed to these drugs, and second, they must accumulate over time, to allow expansion of microbleeding into a symptomatic ICH during antithrombotic therapy.

CMBs are common in populations likely to be exposed to antithrombotic drugs

In population-based studies, CMBs have been reported in between about 5% and 25% of older people: this wide range in prevalence is likely to reflect differences in sensitivity of the MRI techniques and age of populations. Evidence is emerging for a different distribution of CMBs depending on ethnicity: in Caucasians most

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CMBs are located in lobar regions,^{17,18} suggesting CAA as a dominant cause. By contrast, in Asian cohorts, deep CMBs, probably indicating hypertensive arteriopathy, predominate.¹⁹

CMBs are also common in populations with neurological disease, including patients with cognitive impairment,²⁰ ischaemic stroke,²¹ ICH,²² CAA and Alzheimer's disease²³ as well as the rare genetic cause of stroke, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).²⁴ CMBs are more common in recurrent than first-ever

stroke, suggesting that they may reflect the progression of underlying small vessel disease. In stroke cohorts, the highest prevalence for CMBs is in individuals with recurrent ICH.²⁵ In ischaemic stroke, the hypothesis that CMBs reflect small vessel disease is supported by preferential associations with ICH and lacunar infarction as

CMBs develop over time

bolic ischaemic stroke.²⁶

Table 2 Criteria for defining cerebral microbleeds (from Ref. 4)

- 1 Black lesions on T2*-weighted MRI
- 2 Round or ovoid lesions (rather than linear)
- 3 Blooming effect on T2*-weighted MRI*
- 4 Devoid of signal hyperintensity on T1- or T2-weighted sequences
- 5 At least half the lesion surrounded by brain parenchyma
- 6 Distinct from other potential mimics such as iron or calcium deposits
- 7 Clinical history excluding traumatic diffuse axonal injury

MRI, magnetic resonance imaging

'The blooming effect on MRI refers to the
observation that CMBs as seen on T2"-weighted
brain imaging are larger than their actual size
(or their size if they are seen on standard
structural MRI [e.g., T2-weighted images]).
By Increasing the TE (Echo Time) on a T2"
weighted GRE, the dephasing period is increased
and the blooming effect is increased

at baseline

CMB, cerebral microbleed

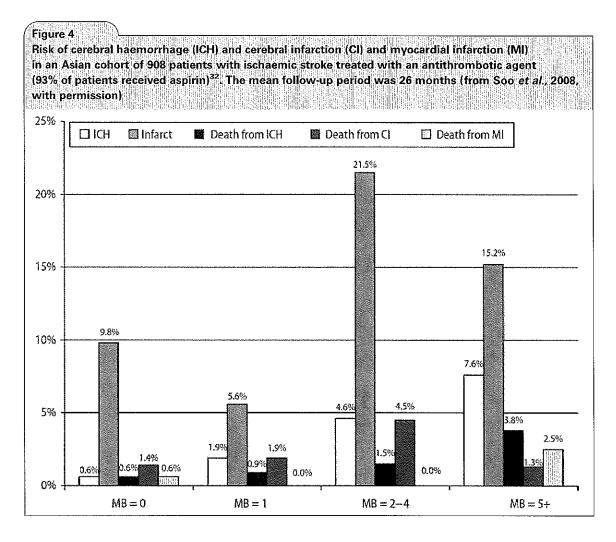
The incidence of new CMB over about three years in the Rotterdam study was 85/831 patients (about 10%).²⁷ In another study of a cohort of memory clinic patients, the incidence of CMB was 12% over about 2 years. 28 In a small stroke clinic population, new CMBs were noted in five of 21 patients over five years, and their development was strongly related to baseline systolic blood pressure and, as in the other studies (ref 27,28), the presence of baseline CMBs.²⁹ A larger study of 224 patients with stroke or TIA found that over a mean follow-up period of 27 months new CMBs developed in 10 patients (6.8%). The estimated annual rate of change of CMB numbers was 0.80 lesions per year in all patients, but the rate was more than 5% per year in patients with more than five CMBs at baseline, 30 suggesting a graded increase in risk according to CMB burden.

compared with atherothrombotic or cardioem-

CMBs as a predictor of future stroke risk

High-quality prospective data on how CMBs relate to future stroke risk are scarce. Table 3 summarizes key results of the main available prospective cohort studies. These studies, show an increased risk of recurrent stroke, mainly ICH, in patients with CMBs (with a greater risk if CMBs

Study	Year	Proportion of patients with CMB	Follow-up duration	Incidence of ischaemic stroke in individuals with CMBs	Incidence of ICH in individuals with CMBs
Thijs <i>et al.</i>	2010	129/487	2.2 years	10% (P= 0.054)	0.8% (P = 0.09)
Fan et al.	2003	43/121	27.15 ± 11.68 months	11.6% ($P = 0.841$)	9.3% (P = 0.053)
Soo et al.	2008	252/908	26.6 ± 15.4 months	9.6% (0 CMB), 5.6% (1 CMB), 21.5% (2-4 CMB) 15.2% (≥5 CMB) (P = 0.226)	0.6% (no CMB), 1.9% (1 CMB), 4.6% (2-4 CMB 7.6% (≥5 CMB) (P < 0.001)
Boulanger et al.	2006	45/236	14 months (median)	20.3% (P = 0.039)	3.3% (P = 0.31).



are multiple).31-33 By contrast, a Canadian study of ischaemic stroke or TIA found an increased risk of ischaemic stroke rather than ICH.34 In a small prospective study of 21 surviving patients with ischaemic stroke or TIA followed up after a mean interval of 5.5 years, the investigators found only one recurrent ICH among eight patients with CMBs, compared with no ICH in 13 patients without CMBs. 29 A European cohort of 487 patients with a TIA or ischaemic stroke, also found that patients with microbleeds had a higher risk of developing new ischaemic stroke rather than ICH.35 Interestingly, only strictly lobar CMBs (or combined with deep microbleeds) had an independent effect on the risk of recurrent stroke (P = 0.018) in this study, suggesting that CAA may be a risk factor for ischaemic stroke as well as ICH.

The largest prospective study of CMBs in stroke patients to date comes from an Asian population of 908 patients with ischaemic stroke or TIA^{32} . The investigators prospectively evaluated patients with pre-existing CMB (27.8%) and compared the risk of developing ICH, ischaemic stroke and mortality. The found an increased risk of ICH which directly correlated with the number of pre-existing CMB (0.6% [no CMB], 1.9% [1 CMB], 4.6% [2–4 CMB] and 7.6% [\geq 5 CMB]), and also showed a future ischaemic stroke risk of 9.6% (0 CMB), 5.6% (1 CMB), 21.5% (2–4 CMB) and 15.2% (\geq 5 CMB) (Figure 4).

CMBs also influence future ICH risk after symptomatic ICH. Greenberg *et al.*^{36,56} prospectively evaluated a cohort of CAA patients with lobar ICH, and found that the count of microbleeds or macrobleeds on baseline MRI predicted

an increased risk of haemorrhagic stroke (proportional to the count) in survivors. Jeon *et al.*³⁷ also noted an elevated risk of recurrent ICHs development associated with CMBs (but not with other clinical and laboratory data), in a prospective study of 112 survivors of ICH.

The predictive value of CMBs for the risk of occurrence of symptomatic cerebrovascular disease in the general population is largely unknown. One recent large-scale prospective study of 2102 healthy elderly individuals followed for a mean interval of 3.6 years in Japan³⁸ demonstrated a significant association between CMBs and subsequent ICH (hazard ratio: 50.2; 95% confidence interval [CI]: 16.7-150.9) and ischaemic stroke (hazard ratio: 4.48; 95% CI: 2.20-12.2). These findings are of interest, but it should be noted that the CIs around the risk estimates are wide, and the findings await confirmation in other longitudinal population-based studies, ideally in a range of different populations to reflect the spectrum of small vessel disease across ethnic groups.

In summary, increasing evidence suggests that CMBs are a risk factor for the risk of future stroke. Some, but not all studies, adjusted for potential confounding factors (e.g. age, hypertension). The available data suggest that overall the risk may be higher for ICH than for ischaemic stroke, but this balance may depend on the characteristics of the population studied (e.g. Asian versus non-Asian). Further studies are required to clarify this. However the critical question for clinicians is whether the risk of future ICH is increased by the presence of CMBs, and whether any increase in risk is sufficient to tip the balance away from recommending antithrombotic drug treatment.

CMBs and their implications for antithrombotic therapy

Antiplatelet drugs, CMBs and ICH risk In ischaemic stroke from causes other than cardiac embolism (in which anticoagulation is generally preferred), antiplatelet medications are a key component of secondary prevention of future occlusive vascular events. Aspirin is the most widely studied agent, and carries only a small absolute risk of symptomatic ICH of less than 0.5%, 39 though this risk seems to be higher in Asian

than in non-Asian cohorts. There has been concern that antiplatelet drugs could not only cause CMBs but also increase the risk of symptomatic ICH.

Cross-sectional studies. A number of crosssectional studies have evaluated associations between antiplatelet exposure and the presence of CMBs, but CMB presence may be confounded by some indications for antiplatelet treatment (e.g. a history of ischaemic stroke). Nevertheless, the Rotterdam Scan study in over 1000 healthy elderly individuals found that prior antiplatelet use was associated with an increased prevalence of CMBs (odds ratio [OR]: 1.71; 95% CI: 1.21-2.41), a finding which persisted after adjusting for potential confounders including history of stroke.⁴⁰ The same study also noted that strictly lobar CMBs were more common in aspirin users than those using an alternative antiplatelet drug, carbasalate calcium (OR: 2.7; 95% CI: 1.45-5.04), suggesting that aspirin may specifically aggravate microbleeding in the context of CAA. Our small hospital-based UK case-control study⁴¹ found that CMBs were more likely to be present in ICH patients who were on antiplatelet therapy compared with both ICH patients without antiplatelet therapy and to matched non-ICH patients on antiplatelet therapy; lobar CMBs were found in 69% of the ICH group compared with 33% of the control group of antiplatelet users without ICH (P = 0.03). After adjustment for leukoaraiosis, the presence of lobar (but not deep) CMBs was a significant predictor of antiplatelet-related ICH (OR: 1.42), also supporting an interaction between aspirin use and CAA. One small prospective study in CAA showed a high risk of recurrent ICH, with evidence that this risk is increased risk by aspirin treatment.36 Thus, CAA may be an important risk factor for antiplatelet-related ICH, but because of the small sample sizes to date, further data are required to confirm this.

Three studies in eastern Asian countries have also shown a higher prevalence of CMBs in antiplatelet treated patients. Jeong *et al.*⁴² evaluated 187 patients with primary ICH in order to determine associated risk factors and clinical and radiological correlates. They found the use of antiplatelets and anticoagulation to be associated with an increased risk of ICH in patients with CMBs. In a retrospective study comparing a small Asian cohort of 21 aspirin users who developed ICH

with healthy matched controls, Wong et al.43 found a much higher proportion of CMBs in the ICH group (CMBs were found in 19 cases compared with only 7 of 21 matched aspirin users without any history of ICH [P < 0.001]). Ge et al.44 retrospectively looked at 150 cases of ischaemic cerebrovascular disease patients on Aspirin and matched controls not taking Aspirin and found an increased frequency of CMB (40% versus 12%; OR: 4.899; P < 0.0001) and ICH (28% versus 1%; OR: 28.778; P < 0.0001) in Aspirin users. By contrast, in a Japanese cohort of ICH patients with underlying pre-existing white matter changes, there was an association of CMB with ICH but not with antiplatelet use. 45 A systematic review in a mixture of Asian and non-Asian cohorts including data from 1461 patients with ICH and 3817 with TIA or ischaemic stroke also found that CMBs were more common in antiplatelet users than in non-users with both ICH (OR: 1.7; 95% CI: 1.3-2.3) or ischaemic stroke (OR:1.4; 95% CI: 1.2–1.7).46

Prospective studies. Prospective data on CMB presence and future ICH risk on antiplatelet treatments remain scarce. The largest study published to date, as previously mentioned, is from Asia (Hong Kong), where 908 patients with ischaemic stroke treated with a single antithrombotic agent (in 93% of cases aspirin) were screened for CMBs and followed up for a mean period of 26 months.³² CMBs were found in 28% of patients, most often in deep regions suggesting hypertensive arteriopathy as the most likely cause. The risk of ICH was higher in individuals with baseline CMBs, and increased with increasing CMB count. These data suggest that CMB presence and number of CMB are relevant for ICH risk in this Asian population. CMBs were also associated with an increased risk of ischaemic stroke, but this did not show a graded relationship with CMB count at baseline. Given that antiplatelet agents have only a modest effect in secondary ischaemic stroke prevention (absolute risk reduction approximately 1-2% per year),47 an ICH risk of 7.6% in those with >5 CMBs may outweigh the benefit in this subgroup of patients. However, it is not known whether these data are generalizable to non-Asian populations.

In summary, there are robust associations between antiplatelet use and the presence of CMBs, but cross-sectional studies cannot fully adjust for

potential confounding factors. The largest available prospective study (in an Asian population) suggests that CMBs may also influence the future risk of ICH in ischaemic stroke patients treated with antithrombotic drugs. However, since the overall benefit of antiplatelet treatment has been established in very large randomized trials and meta-analyses, there is currently insufficient evidence to recommend withholding them in patients with CMBs. There are very few data relating to the use of multiple antiplatelet agents together, but these could pose a greater risk than single antiplatelet treatment in individuals with small vessel disease.⁴⁸ Screening for CMBs should be considered for future antiplatelet randomized trials or natural history prognosis studies after stroke.

Anticoagulant drugs, CMBs and ICH risk Ischaemic stroke is a common consequence of atrial fibrillation, and the risk increases with the presence of other risk factors including age, hypertension, congestive heart failure and diabetes. Anticoagulation with Warfarin⁴⁹ and newer agents including Dabigatran⁵⁰ and Rivaroxaban⁵¹ are all very effective in reducing the risk of ischaemic stroke by about 60-70%. Nevertheless all anticoagulants inevitably increase the risk of unwanted bleeding: the most feared of all complications from anticoagulation is ICH. Conventional anticoagulation in ischaemic stroke patients increases the risk of ICH up to 7-10-fold with an absolute risk of about 1% per year.⁵² The risk of ICH is generally higher in inception observational cohorts in comparison to clinical trials, from which many high-risk patients are excluded.⁵³

Despite the clear efficacy of anticoagulants for stroke prevention, the proportion of ICH related to the use of anticoagulant drugs has increased in recent years: about 15% are currently related to warfarin use. The increasing use of anticoagulants in elderly populations is expected to result in an increasing incidence of anticoagulant-related ICH. There is thus major interest in whether new imaging or genetic biomarkers may help to predict the risk of this rare yet devastating and unpredictable complication. Because oral anticoagulant associated ICH is associated with increased age and previous stroke, and often occurs with anticoagulation intensity within the therapeutic

Figure 5

(a) Two simultaneous warfarin-related intracerebral haemorrhages in an elderly patient with atrial fibrillation. (b, c) T2*-weighted gradient-recalled echo reveals the presence of multiple strictly lobar cerebral microbleeds (some shown with arrowheads), consistent with underlying cerebral amyloid angiopathy. Note that the symptomatic haematomas are also lobar

(a) T2*-GRE

(b) T2*-GRE

(c) T2*-GRE

range, it is likely that mechanisms underlying high risk relate to individual patient factors, for example an age-related disorder of small brain blood vessels. There is evidence that patients with CAA have a particularly high risk of anticoagulant-related ICH (Figure 5).⁵⁵ Patients with symptomatic lobar ICH suggestive of CAA have annual recurrent ICH risk of up to about 20%,^{36,56} and anticoagulants appear to increase this risk, as well as increasing the clinical severity and mortality rate from ICH.⁵²

Since MRI is the most sensitive way to image the consequences of small vessel disease,⁵⁷ some studies have investigated whether it may be useful in risk stratification. Leukoaraiosis - a confluent deep white matter abnormality seen as low attenuation on computed tomography (CT) or high signal on T2-weighted MRI, and a marker of small vessel disease - increases the risk of oral anticoagulant-related ICH.58 CMBs provide direct evidence of leakage of blood from pathologically fragile small vessels, so might be a better predictor of oral anticoagulant-associated ICH than leukoaraiosis alone. In the current stroke risk scoring systems (CHA2DS2-VASc for thrombotic risk⁵⁹ and HAS-BLED for bleeding risk)⁶⁰ paradoxically, some of the risk factors for future ischaemic stroke risk are similar to those associated with increased bleeding risk (age, previous stroke, hypertension). Neuroimaging and genetic biomarkers that are more predictive of ICH than ischaemic stroke hold promise for refining the risk-benefit assessment in this situation.⁶¹ Although CAA defined by symptomatic ICH is generally considered to be a contraindication to anticoagulation, it is not known whether the presence of lobar CMBs alone (without macrohaemorrhage) is a risk factor for ICH. There are few pathological validation studies to confirm whether lobar CMBs are sufficient to diagnose CAA. Below we briefly discuss the limited data relating to CMBs and anticoagulant bleeding risk.

Cross-sectional studies. There are few crosssectional studies addressing the potential role of CMBs in anticoagulant-related ICH. One casecontrol study included 24 ICH patients with warfarin use compared with 48 warfarin users with no history of ICH and found a greater number of CMBs in the ICH group; prothrombin time and CMB presence were predictive of ICH.⁶² A Chinese study also demonstrated an association of CMB in ICH patients previously on Warfarin.⁶³ By contrast, a Turkish study of anticoagulated patients did not find a significant difference in CMB prevalence between Warfarin users versus non-users.64 In a systematic review and meta-analysis of cross-sectional data mentioned above⁴⁶ the authors found an 8 fold increase in the OR of having at least one CMB in warfarin treated ICH patients compared with ICH patients not taking warfarin.

Prospective studies. There are no reliable large-scale prospective data regarding the effect of CMBs on the risk of ICH in patients with

Study	Year	No. of patients	SICH rate in CMB group	SICH rate in non-CMB group
Fiehler et al., BRASIL study	2007	570	5.8% (95% CI, 1.9-13.0)	2.7% (95% CI, 1.4-4.5)
Derex et al. ⁷⁸	2004	44	1/8 patients (12.5%) non-significant	3/36 patients (8.33%) non-significant
Kim <i>et al.</i>	2006	65	8/25 (32%) non-significant	9/40 (22.5%) non-significant
Kakuda <i>et al.</i> ⁷⁹	2005	70	0/11 (0%) non-significant	7/59 (11.9%) non-significant
Kidwell et al.80	2002	41	1/5 (20%) non-significant	4/36 (11.1%) non-significant

previous ischaemic stroke and atrial fibrillation treated with warfarin, who in clinical practice pose perhaps the greatest dilemma for treatment. Until high-quality data about the magnitude of risk are available anticoagulation should continue to be recommended for patients with atrial fibrillation regardless of the presence of CMBs, based on the compelling results from large randomized trials and meta-analyses. The question of how CMBs may affect future ICH risk after anticoagulation in the setting of acute cardioembolic stroke is being investigated in UK-wide prospective multicentre inception cohort study, CROMIS-2 (www.ucl.ac.uk/cromis-2). Clinicians are encouraged to participate in this and other observational studies to allow a more definitive recommendation about anticoagulation in patients with CMBs to be made. 65 Although the newer anticoagulants have lower rates of ICH, the effects of small vessel disease on this risk and how the data from trials translate to day-to-day practice remain unknown.

Statins and CMBs

Some studies have found an association between low serum cholesterol and increased CMB burden, ⁶⁶ although in patients with acute ischaemic stroke or transient ischaemic attack previous statin therapy was not associated with either the prevalence or the burden of CMBs. ⁶⁷ A higher risk of ICH was observed in atorvastatin-treated patients in secondary prevention trials of patients with ischaemic cerebrovascular disease (SPARCL): the hazard ratio was 4.1 for those entering

following ICH compared with 1.6 for those enrolled with ischaemic stroke, which suggests a possible relationship between statins and intracerebral bleeding.⁶⁸ Although a case-control study found statin use prior to ICH to be associated with reduced mortality and favourable outcome, in line with a meta-analysis, 69 others have noted an association between low LDL cholesterol levels and increased mortality.70 These inconsistent associations do not allow a definitive recommendation to be given on statin therapy in the context of CMBs. A decision analysis suggests that CMBs in the context of CAA (e.g. multiple areas of strictly lobar cerebral haemorrhage) should lead to avoidance of statins, since they indicate a high risk of future ICH. 71 However, this decision analysis is not a substitute for observational or randomized evidence, both of which are needed to determine the true risk of statins in individuals with CMBs.

CMBs and Thrombolysis in Acute Ischaemic Stroke

The most widely used effective treatment for acute ischaemic stroke is intravenous thrombolysis. The most devastating complication is ICH,⁷² which may have a devastating impact on the patient. Leukoaraiosis, a marker of cerebral small vessel disease, is associated with an increased risk of ICH.⁷³ CMBs, as a potential marker of bleeding-prone small vessel diseases, have long been suspected as a new risk factor for post-thrombolysis ICH. The available studies on this topic are summarized in Table 4. The largest of these studies

(BRASIL),74 prospectively evaluated the risk of symptomatic ICH (defined as a clinical deterioration with an increase of 4 points on the NIHSS score, and a temporal association with parenchymal haematoma) found a non-significant increase in the risk of symptomatic ICH in patients with CMB (symptomatic ICH risk was 5.8% [95% CI, 1.9 to 13.0] in the CMB group as compared with 2.7% (95% CI, 1.4 to 4.5) in patients without CMBs [P = 0.170]). Similarly, Kim et al.⁷⁵ investigated 65 patients with varying numbers of CMBs (CMBs were subdvided into four grades: I - [CMB absent], II - [1-2 CMB], III - [3-10 CMB and IV – greater than 10 CMB] and did not demonstrate that the presence or burden of CMBs were independently associated with the risk symptomatic ICH after thrombolysis).

Two recently published meta-analyses suggest a trend towards increased risk of symptomatic ICH in thrombolysed ischaemic stroke patients, ^{76,77} but acknowledge the limitations of the available studies (e.g. non-standardized or insensitive MRI techniques, small sample sizes, varying ICH definitions). Clearly, further larger and well designed studies are urgently needed to answer this dilemma posed by CMBs.

Conclusion

CMBs are not just an incidental finding revealed by new neuroimaging technology. Current literature suggests at least two different underlying arteriopathies causing different topographic patterns of CMBs (hypertension, leading to deep CMBs, and CAA, leading to strictly lobar CMBs). In clinical practice the distribution of CMBs is mixed, suggesting that these two arteriopathies often coexist or interact. The core question that persists is whether CMBs are associated with an increased risk of ICH or ischaemic stroke or both? And if so, is this risk modified or enhanced with the concomitant administration of antiplatelets and anticoagulation therapy. Current data, both prospective and crosssectional, suggest an increased stroke risk in the presence of CMBs. The risk of ICH may be higher than the risk of ischaemic stroke, but population ethnicity (Asian versus non-Asian) may play a role in this balance of risk. There is consistevidence of an association between antithrombotic use (mainly relating to antiplatelet drugs) and CMBs in cross-sectional studies, and limited prospective data suggesting an increased hazard for antiplatelet drugs if CMBs are present. Few data are available on whether CMBs influence the risk of ICH during anticoagulation after ischaemic stroke. Since cross-sectional data are unable to prove causation there remains an urgent need for larger prospective studies, in a range of populations, to specifically investigate the risks of ICH associated with CMBs. Until clear and consistent data are available to show an increased hazard of CMBs, clinicians should continue to recommend antithrombotic therapy after ischaemic stroke or TIA based on the results of large randomized trial and meta-analyses. In patients with previous symptomatic ICH and evidence of CAA, antithrombotics should be used with particular caution, and only when clear treatment indications, that are judged to outweigh the very high ICH risk, are present.

Summary points

- CMBs are an important neuroimaging finding on a T2* GRE MRI scan and are indicative of underlying small vessel damage; they correspond to perivascular haemosiderin deposits, which are presumed to be due to small areas of bleeding from small vessels;
- The distribution of CMBs reflects the underlying type of microangiopathy – hypertensive arteriopathy (deep CMBs) or CAA (strictly lobar CMBs);
- People with pre-existing CMBs are likely to develop more CMBs over time;
- In stroke patients (both ischaemic stroke and ICH), CMBs are associated with an increased risk of future ICH and ischaemic stroke, independent of potential confounding factors;
- The presence of CMBs in patients with ischaemic stroke (including those treated with antiplatelet agents) is associated with an increased risk of future stroke (ICH risk>ischaemic stroke risk). CAA may be a particular risk factor for ICH on anticoagulant or antiplatelet drugs. However, current data are insufficient to recommend with holding antiplatelet drugs in patients with CMBs. Although CMBs are associated with anticoagulant related ICH in

- cross-sectional studies, there are no large-scale prospective studies of CMBs and ICH risk after anticoagulation;
- The role of CMBs in predicting thrombolysisrelated ICH risk in ischaemic stroke is currently uncertain; there is a non-statistically significant trend towards increased ICH risk if CMBs are present prior to thrombolysis, but the clinical relevance is not yet established and requires further study.

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EXHIBIT 25

From the Birmingham Business Journal :http://www.bizjournals.com/birmingham/stories/2001/07/02/story2.html

NFL Europe's injured flown to Birmingham

Jul 1, 2001, 11:00pm CDT

Gilbert Nicholson Staff

When a player in the NFL Europe League gets seriously injured, he's carted out of the stadium to a jumbo jet for a flight back to the United States. To the Football Capital of the South, to be exact.

The player's destination is HealthSouth, the Birmingham-based national rehabilitation hospital and clinic chain, which has a contract with the spring football league.

"We're real proud we've been able to bring the medical liability of the league down from \$2.7 million in 1996 to between \$900,000 and \$1 million," says HealthSouth's Mayfield Armstrong, head athletic trainer for NFL Europe.

Armstrong has been working with the sports organization since its inception in 1991, when it was first called the World League of American Football, a developmental league for the NFL.

HealthSouth personnel have worked with about 70 players this year from the six-team European league, which this weekend plays the season-ending championship game in Amsterdam, dubbed the World Bowl. Thirty rehabilitated players have rejoined their teammates in Europe this season.

"We're managing the care of 400 professional football players, all employees of the same company who we teach to line up and knock the other guy down so he won't get up. It's a workmen's comp nightmare," Armstrong guips.

Players whose injuries are expected to keep them off the field for more than two weeks typically make the trip to Birmingham.

"Europe has excellent fracture and trauma people, but they're still behind us as far as sports medicine is concerned," Armstrong says.

A player's flight to Birmingham involves more than a comfy seat and a beverage,

"We just don't put a guy on a gurney and fly him back home," Armstrong says. "We don't want to put him on a plane for nine hours with a swollen (knee) joint. We'll immobilize his leg to keep it straight."

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Given the cramped seating aboard airplanes, that can be a challenge.

"The airlines accommodate us well. We have to give them some notice, and with help from the skycaps, they'll usually move a guy to business class."

Hurt on first play

One such player is Troy State grad Mareno Philyaw, 23, a receiver for the Barcelona Dragons who was allocated to Europe by the Atlanta Falcons.

"It was the first play of the first game of the season," Philyaw says, recalling that April 21 game against the Berlin Thunder. "I was on the kickoff return and a guy got hit and fell back in to my knee. I thought it may have just been a sprain."

An MRI, however, showed that Philyaw's ACL ligament was torn.

"It shook me up a little," he says. "I was a little bit disappointed. But I have to say that's part of the game."

A week later, Philyaw was in Birmingham for surgery and rehab.

Philyaw's toughest rehab exercise involves walking along a balance beam while snagging footballs tossed at him in rapid-fire fashion. Sound tough? It gets worse: A HealthSouth trainer is trying to pull him off with a rope attached to Philyaw's waist.

"Every now and then they'll get me off the beam," he says. "It's a good thing the beam is close to the ground."

Before being released, players undergo a rigorous exam that includes computerized testing. One exam, called the biodex test, measures leg strength in hundredths of percentage points.

"We (expect) the injured leg to be within 85 percent of the strength and agility of the well leg," Armstrong says.

Players are released only after getting the green light from Dr. Larry Lemak, a founding partner of Alabama Sports Medicine and Orthopedic Center who plays a key role with HealthSouth's NFL Europe efforts .

Two weeks ago Philyaw was sent to his home in Atlanta to continue rehabilitation at a HealthSouth facility there.

Armstrong, meanwhile, has just returned from Europe where he conducted exit physicals.

"If anyone is still hurting at the end of the season, they'll come to Birmingham for further treatment before they're allowed to go back to the NFL team that allocated them. Or, if they're a free agent and have no commitment, they're allowed to go home," he says.

"If you spend a little money on a plane ticket and have a good outcome where you can close the door on a complaint, it saves the NFL a lot in liability at the end" of the season," he says. 10/1/2014

Casea18-2012mdDacNffaente Contra 30001213321655500124 Pragitie 41140/06/104124 Pring 8:5008/05/2019 Contact reporter Gilbert Nicholson at (205) 443-5632 or by e-mail at gnicholson@bizjournals.com.

EXHIBIT 26

The New York Times

September 15, 2012

A Player's Concussion, a Family's Ordeal **BV JUDY BATTISTA**

FORT WORTH — Mitch White watched football last Sunday, a framed New Orleans Saints jersey mounted on a wall over his shoulder at his home. White watches football differently from most people. He likes to analyze the offensive line, fitting for a tackle out of Oregon State who was a sixth-round draft pick of the Saints in 2001. And on most days, around the hour the early games reach halftime, White needs to lie down for a nap.

The Saints jersey has its spot, but there were other stops with other teams, too, so many that White sometimes is confused about what order the teams came in and who the coach was. Everywhere it was the same, though. White never played in a regular-season game, always stopped by a freakish injury, a newly signed player, or even one extended battle with the staph infection known as MRSA. After that, White asked the Tampa Bay Buccaneers to allocate him to N.F.L. Europe, now defunct, hoping it would help him get back into shape. White was a journeyman backup and practice squad player, on perhaps the most anonymous rung in the N.F.L. player hierarchy, trying to hang on to his career.

Now, seven years and one crushing hit later, he is one of the more than 3,000 former N.F.L. players who are suing the league over concussions. At 34, White is unable to work and is sometimes so debilitated by migraines that he cannot care for his two young daughters. He takes as many as eight medications at a time to ease his headaches, to smooth his erratic moods, to soothe his sleeplessness. He spends much of his time exploring treatments to find relief that rarely lasts longer than a few days: Botox injections, massage, sensory deprivation.

White and perhaps just a few hundred plaintiffs like him did not enjoy much of the glory or the riches that playing on Sundays usually bring. But they suffered the damage that they believe is the N.F.L.'s calling card, too.

In White's case, it was one hit at an N.F.L. Europe training camp in March 2005, when a blitzing middle linebacker crashed into the right side of White's head as White was pulling from his right tackle position. That sent him tumbling to the grass, knocking him out for a few moments and altering him so ineffably that his mother said, "When he first came home, it was like my son was gone."

To see White now is to get a glimpse of the challenges of living with the effects of a head injury.

10/1/2014 Case 132 2012-rfe 100 20 10 20

He looks healthy, back down to his high school weight of 245 pounds, down from his high N.F.L. weight of 335. He and his family live in a comfortable house with a big portrait of their daughters on a mantle, in a well-maintained subdivision. This was a good day, his wife, Jennifer, said, meaning he got some sleep and had restrained himself from physical activity enough — a workout at the gym can set him back for three days. The headache, while there from the moment he woke up, was at least tolerable until midafternoon.

But after 90 minutes of talking, White's energy waned. His speech became more deliberate. Sitting on his sofa, he shaded his eyes from the overhead lights in his living room. He gets lost if he drives more than a few miles from home.

The Whites were recently out to dinner with friends, and after two hours, White said he could not talk or think normally. When they have plans, White said, he will load up on medication and try to get through it. Or they will simply cancel. He used to be really funny, he has told his wife. He misses that, she said.

"I try to act normal," White said. "I just want to be normal."

White did not start playing football until he was 16 as a high school sophomore, and he does not remember sustaining any concussions in high school or college. The hit that injured him, White said, was not even the hardest one he had ever taken, although he thought his helmet was not inflated properly.

"I tried to stand up, and fell over — I did that like twice," White said, sitting in his living room, which is usually kept cool and dark because heat and light can make his headaches worse. "A lot of people have told me — I don't remember like two or three days after that — I guess I walked up to the huddle, I thought I was in the huddle, but I was three feet behind the huddle.

"All I remember is I went back in. I just remember being in my stance and trying to lift my head up, and it was excruciating."

White's odyssey through postconcussion life winds through doctors and hotel rooms, starting first in Tampa, Fla., when he was given Tylenol and Advil for his relentless headache, but still told to go to meetings and watch practice the next day. The nadir came during three months in Birmingham, Ala., where players with longer-term injuries were sent. One doctor told him he had a mild concussion and should be ready to go in another week or so. But he could not sleep. He was made to run at one point, and ended up vomiting. He spent most of his time alone, in a dark hotel room.

"I wasn't thinking clearly at all," White said. "I was severely depressed. I had suicidal thoughts,

10/1/2014 Case 132 2012-rfe 100 20 10 20 big time. It just kept popping in my head. I was thinking of hanging myself with shoe string, or every time I was in a car, I had an urge to jump out of the car on the freeway.

"I knew that was wrong. I couldn't control it."

A neurologist finally told White that the concussion he had was more moderate to severe. Later, a doctor in Pittsburgh was irate that White had been isolated in Birmingham. He told White to go home, to be around family members who could be supportive.

His mother called that time "a disaster." She and Mitch fought, and he had mood swings. "It was like he had a void in his eyes, there was no emotion," his mother, Donna Stacy, said.

Finally, doctors told White he would never play football again. He was stunned.

"I was waiting to get better," he said. "It's just the mentality; you just want to be in there, you feel like you're letting your friends down. I just thought it was like a knee injury. Rehab and get better and go. It was extreme depression."

White worked briefly with his brother in a food delivery service. But working a full day made his headaches worse and led him to take more migraine medicine than he was supposed to. He had to cancel meetings and lie on his office floor when the migraines struck. After about six months, he stopped altogether.

"It drives me crazy just sitting around," White said. "We are meant to work."

White was able to live off savings for about a year, and now he receives about \$8,000 a month in payments from the N.F.L. and players union funds. His closest friends understand why White stays at home. But the mothers who take their children over to play with his daughters sometimes may wonder why he is in bed, he said.

White met his wife after he was injured, and everything about their lives together is clouded by his health. Jennifer White works the overnight shift as a registered nurse two days a week, so she is home to help care for their children. When she is not there, he calls his mother or mother-in-law for help.

Jennifer White is due to give birth to a son this year, and she doubts her husband will be able to care for three children. Stacy lives about 20 minutes away, but she is considering moving closer.

Some people have asked why they are having another child, given the situation, and Jennifer White replies: "We're not going to not have children. We're trying not to let it take over."

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Jennifer White would like to guit working when their son is born, but they count on her job for medical insurance. One of Mitch White's doctors, Gary Tunell of Texas Neurology, hopes that eventually, White will not have to take so much medicine, but Tunell cannot guarantee that White's symptoms will get substantially better.

"That this has gone on seven years makes you more doubtful," Tunell said. "I think they will be diminishing in severity over time. I've tried to get Mitch to carry on normal activities. He needs to do some form of progressive exercise, and try to work through these headaches. Because right now, they are controlling his life."

The Whites have not given up hope that some new treatment might work. But the awful possibilities loom, every day.

"What he fears is early-onset Alzheimer's," she said. They do not expect much money from the lawsuit, although White is convinced that the league concealed for years its knowledge of the potential risks for players. They hope that improved education about concussions will prevent someone else from going through what White has.

Last month, the N.F.L. filed a motion to have the lawsuits dismissed, arguing that they should be resolved under the terms of the collective bargaining agreement and not by the courts.

"The N.F.L. has long made player safety a priority and continues to do so," the league said in a statement. "Any allegation that the N.F.L. intentionally sought to mislead players has no merit."

As for White, he said he would let his son play football. "I don't hate the N.F.L.," he said. "I love the sport. I in no way want to damage the league. I just thought I'd get better eventually. I had no idea this could be for the rest of your life. That this will affect you, your family, your wife.

"I expected to be hurt. I knew there was a possibility I could be paralyzed. Did I know I could get brain injury and be like this? No. I couldn't fathom that happening."

EXHIBIT 27

The New Hork Times http://nyti.ms/1udgSF4

PRO FOOTBALL | ANALYSIS **NYT NOW**

For Retirees, Decision on Concussion Settlement Will Not Be a Simple One

N.F.L. Concussion Settlement Divides Former Players

By KEN BELSON JULY 22, 2014

> Class-action settlements are often messy. When enough aggrieved people are thrown together, it is natural that some of them will be unhappy with a deal that is a result of a negotiation between parties trying to avoid a long, expensive trial with an uncertain outcome.

The proposed settlement in the case brought by more than 4,500 retired N.F.L. players who claim the league hid from them the dangers of concussions is similar. Asking 10 retired players what they think of the settlement might elicit 10 opinions.

In the coming weeks, though, the 20,000 retired players and their beneficiaries will have to make a final decision to accept the proposed deal, which includes an unlimited number of cash awards for a small set of severe neurological conditions; to opt out and perhaps sue the league for more; or to object and possibly appeal the settlement.

To make informed choices, retired players will have to pore over the settlement, consult their lawyers and doctors and consider their own health and financial needs. They will also have to weigh a host of arguments for and against accepting the plan.

Jeff Nixon, who played for the Buffalo Bills from 1979 to 1982, is among those who view the settlement as the best of several bad options. Going to trial, he said, was no slam dunk because the players would have to clear

several significant legal hurdles, most notably the league's argument that the collective bargaining agreement governed player injuries.

"The lawyers fought as hard as they could and got as much as they could from the settlement," said Nixon, who writes a blog about the settlement. "To continue litigation was pretty risky."

The settlement, he said, will get money into the hands of the former players who are in the worst shape, such as those with Parkinson's disease or Alzheimer's disease, and will act as an insurance policy for players whose health might deteriorate.

"We didn't get everything we wanted, but we got the N.F.L. to say, 'We'll give you guys money if you have symptoms,'" he said. "The bottom line is if you've got impairments and symptoms, you'll get paid."

There are many retired players, though, who say the settlement is irreparably flawed, and seven of them took the unusual step Monday of asking a federal appeals court to intervene to correct what they see as deficiencies.

Sean Morey, Alan Faneca and five other former players argued that most retirees would never see any money because many of their ailments would not be covered by the settlement. "The class, as certified, is doomed," they wrote in their filing.

They noted that players who had been found to have chronic traumatic encephalopathy, or C.T.E., a degenerative brain disease closely related with Alzheimer's disease, and who had died before the settlement was finalized, could receive up to \$4 million. Anyone with a diagnosis of C.T.E. after the settlement was finalized could not receive an award.

Christopher Seeger, one of the lead lawyers for the plaintiffs in the class action, said the objectors had misread the settlement. The families of dead players who were found to have C.T.E. might receive awards because the players could no longer receive a diagnosis. C.T.E. was not included for living players because the settlement would cover those symptoms if they were to develop.

"Going forward, any retired player who is sick with a qualifying

condition will get compensated, as C.T.E. cannot be currently diagnosed in living people," he said. "Whether you have C.T.E. or not, or whether or not you can prove you have C.T.E., if you have symptoms of a qualifying condition, you will be compensated."

Susan Owens, whose husband, R. C. Owens, played for the San Francisco 49ers, the Baltimore Colts and the Giants and died two years ago from Alzheimer's disease, raised another potential inconsistency. Under the settlement, younger retired players would receive larger awards than older players on the presumption that head trauma from playing football, and not old age, had contributed to their severe neurological conditions.

But Owens pointed to research by the Mayo Clinic and others who found that people with early-onset Alzheimer's often get the disease because it runs in their families. Other research, though, has shown that moderate or severe brain trauma may raise the risk of developing Alzheimer's disease.

Owens said her husband might have had Alzheimer's disease years before he received a diagnosis because he did not want to admit he was losing his memory. If he had received a diagnosis earlier, he might have been eligible for more money.

"My husband would never admit to anything," said Owens, who has said she might file an objection. "He was an expert at not letting people know how he was."

Retired players will also have to consider Article XI of the settlement, which essentially says that state and federal governments have the right to recover expenses associated with treatment for a player's illness. If a player were eligible for a \$500,000 award and Medicare had paid \$200,000 to treat his condition, the player would receive only \$300,000.

The problem for players is figuring out how much the government has spent. A liens administrator will be appointed to determine those amounts, but players may not get answers until after the settlement has been completed. That means they may not know what they could receive until it is too late, said Michael Kaplen, a lawyer who represents clients with traumatic brain injuries.

"Unless they know what the numbers are, then how can they decide whether to opt out?" he asked.

Seeger, the plaintiffs' lawyer, said that in other settlements he had worked on, he negotiated a fixed deduction that was drastically lower than the amount that the recipients owed. The government, he said, prefers the certainty of receiving small amounts from every recipient rather than spending years trying to claw back money from many people.

"The government likes these deals because rather than chasing these people individually, they can receive a fixed amount for each disease," he said.

Seeger said he was actively negotiating deductions now.

A version of this article appears in print on July 23, 2014, on page B13 of the New York edition with the headline: For Retirees, Decision on Concussion Settlement Will Not Be a Simple One.

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EXHIBIT 28

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Players wrong on key factor in NFL concussion settlement



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- The attorneys representing the players in the NFL concussion lawsuit are now at work getting the word out to all the retired players affected by the revised settlement. That includes the ones who are getting misinformation or inaccurate information including those publicly claiming that they can't get money from the settlement despite having CTE.

"CTE is not a relevant marker for anything in this settlement. It's the symptoms— if you have all the symptoms that are related to CTE, or the diseases that are related, like dementia and Alzheimer's and ALS, then that determines it," said Christopher Seeger, the co-lead counsel for the more than 5,000 players in the settlement.



Frank Wychek (AP Photo)

"If a player thinks he has any symptoms of it, that's the very reason to stay in the deal," he added. "Proving that it's actually CTE is not necessary."

Several players and observers have challenged the settlement, in court by seven retired players and in <u>published interviews by Hall of Famer Tony Dorsett and others</u>. The settlement was revised on June 25 to uncap the amount available to them, and U.S. District Court Judge Anita Brody gave preliminary approval last Monday.

The challenges center on language that implied that those suffering from the degenerative brain disease chronic traumatic encephalopathy (CTE) would not be eligible for a payment if they filed after the date of the revised settlement, and that they wouldn't get anything at all because the disease still can't be definitely diagnosed before death

That, Seeger said, is a fact about the settlement that "they just get wrong."

Players will be part of the payment pool just for showing the commonly-recognizable signs of CTE, without having to prove they have a disease that is still subject to medical research, widespread theory about the cause, and potential challenges by the NFL and its experts.

"If you get sick, period, you still get paid," he said. "We're telling everybody to go get tested. You'll be in the system. You're protected (by the settlement)."

Seeger, co-counsel Sol Weiss and the legal team specifically fought to make sure CTE was not used to determine eligibility, he said, because they didn't want anyone to challenge players to have to prove they have it—and that it was specifically related to concussions, and then only to ones suffered as an NFL player. It was a hurdle the lawyers did not want to subject players to.

"We're taking that argument out of the equation," Seeger said, adding, "You don't have to prove the causation. If you get sick from these symptoms or illnesses, we're going to assume that it was caused by concussions."

The land mine the players have to avoid, he said, was putting too much on the current testing being done to diagnose CTE in living patients—such as the program at UCLA in which Dorsett, among others, was diagnosed with symptoms last fall. Besides the obvious worries about the health implications, it now has left the notion that the test is definitive when it's still just preliminary research that likely would not withstand a legal challenge.

In addition, retired tight end Frank Wycheck told The Tennessean that he was sure that "I am not eligible to receive a dime" despite his symptoms.

Without referring specifically to any player or his objections, Seeger said that was not true. The class action covers roughly 19,000 retired players, he said, and if they played and are suffering (or believe they will suffer) from the effects of concussions, they are covered.

The challenge, he said, is convincing players not to opt out of the settlement and trying to go it alone in court—and possibly lose a chance at payments or benefits forever. Seeger worries that players might end up "listening to a guy who's been listening to television ads and wants to gather plaintiffs to file a case and make some money off of it.

"If there ever was an opportunity to opt out," he said, "this is not the case to do it."

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EXHIBIT 29

PRO FOOTBALL CONCUSSION REPORT

October 01, 2014

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A Fan's Look at Head Injuries and the Concussion Crisis in Football

The NFL CTE Question



Tony Dorsett may be the current face of the NFL Settlement CTE question (AP)

07.22.14

Plaintiffs attorneys for the former NFL football players are trying to clear up the question of CTE in regard to the proposed concussion settlement. A recent Sporting News piece addressed the controversial issue with the former players Co-lead Counsel, Chris Seeger.

"Seeger, co-counsel Sol Weiss and the legal team specifically fought to make sure CTE was not used to determine eligibility, he said, because they didn't want anyone to challenge players to have to prove they have it—and that it was specifically related to concussions, and then only to ones suffered as an NFL player. It was a hurdle the lawyers did not want to subject players to."

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According to the Sporting News piece, the rationale seems to be that:

- 1. It is still too early to diagnose CTE in living people. The work that is currently being done toward this goal is preliminary and may not have withstood a legal challenge.
- 2. Diagnosis of CTE is not necessary because suffering from the symptoms of CTE may make a player eligible for compensation.

If you get sick, period, you still get paid. We're telling everybody to go get tested. You'll be in the system. You're protected (by the settlement).

- ~ Co-lead Class Counsel Chris Seeger
- 3. Players won't have to prove that CTE came from playing in the NFL. Although this of course is one of the main advantages of the settlement, former players do not have to show causation of their injuries, they also don't have to show it in order to be compensated for the other illnesses (ALS, Parkinson's, Alzheimer's and Dementia) which are listed on the grid.

If a player thinks he has any symptoms of it, that's the very reason to stay in the deal. Proving that it's actually CTE is not necessary.

So moving forward, it will be critical to see if the symptoms of CTE manifest themselves in the diagnoses that the NFL settlement compensates.

In June, concussion plaintiffs lawyers Mike McGlamry and Bruce Hagen <u>hosted a session</u> at Emory University's Alzheimer's Disease Research Center that focused on the diseases and testing that is associated with the settlement.



Plaintiffs lawyers host a medical information session at Emory University

The 1 1/2 hour video has a lot of information about the medical issues including the diagnosis of Level 1.5 and Level 2.0 dementia. Without specific diagnoses of ALS, Alzheimer's or Parkinson's, the 1.5 and 2.0 levels of dementia may be looked at as a sort of catch-all or predecessor to the more specific named illnesses.

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EXHIBIT 30



Seaus to opt out of concussion deal

MARK FAINARU-WADA AND STEVE FAINARU via ESPN

Relatives of former linebacker Junior Seau, whose suicide in 2012 put the NFL's concussion crisis on the national agenda, will reject a proposed settlement between the league and thousands of former players, a lawyer representing the family told "Outside the Lines" on Tuesday.

The decision to opt out means the Seaus will proceed with a wrongful death lawsuit they filed in January 2013. That suit alleges that the NFL concealed the dangers of football-related head trauma over a period of several years. After his death, Seau was diagnosed with chronic traumatic encephalopathy, or CTE, a neurodegenerative disease that has been found in dozens of deceased NFL players.

The announcement, coming on the eve of the 2014 season, is a serious blow to the NFL's efforts to put the concussion issue to rest. It raises the specter of continuing litigation that would pit the NFL against the family of one of its most popular players. Seau, a certain Hall of Famer, played 20 years in the NFL.

"The family want to know why this settlement seems designed for expediency for the NFL and to ensure that information doesn't come out," said Seau lawyer Steven Strauss, a partner in the firm Cooley LLP. "And the Seau family wants the truth to come out. Since this litigation started, there hasn't been one document produced, there hasn't been one deposition taken. It seems very clearly designed to nip this in the bud and not have the truth come out, and that's not acceptable to the Seau family, and it's not acceptable to Junior's legacy."

The settlement received preliminary approval from a federal judge in July. The deal calls for payments to former players who qualify under a complicated system that measures the level of neurocognitive impairment related to diseases such as ALS (Lou Gehrig's disease) and CTE. An initial \$765 million deal was resubmitted after the judge raised questions about whether it provided enough money for the potentially large number of players who qualified. The total payout is now unlimited.

Strauss said the Seaus concluded that the deal does not address several concerns, including adequate compensation for the descendants of the former players. Seau's lawyers filed a previous motion objecting to the first proposed settlement, and Strauss said the revised deal did nothing to address those issues.

Strauss said Seau's family, including his four children, is "not suing for his pain and suffering. They're suing for their own. This settlement doesn't address that."

Under the proposed settlement, relatives of some players found to have CTE qualify for compensation up to \$4 million.

Chris Seeger, an attorney who negotiated the settlement on behalf of the players, noted that those who opt out not only forfeit compensation and medical treatment provided by the deal but also face significant legal hurdles.

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"If Mr. Strauss believes the \$4 million his client is eligible for under the settlement is insufficient, he can choose to permanently forfeit these benefits and face all the significant risks associated with continued litigation," Seeger, a partner at Seeger Weiss LLP, said in a statement. "We would advise any class member against opting out of this agreement, considering the tremendous guaranteed benefits it provides."

An NFL spokesman did not respond to inquiries.

Seeger and other supporters of the settlement have argued that the deal was necessary in part because the case against the NFL is difficult to prove. The players, they noted, will have to show that the brain damage was caused by their years in the NFL even though the players participated in youth, high school and college football. They also will have to prove that the NFL suppressed the link between football and brain damage from players and fans even though that connection was discovered relatively recently.

Strauss repeated concerns that have been voiced by other attorneys, who argued that the negotiations that resulted in the deal lacked transparency. Many believe that the case never should have been treated as a class action because the players and their families have such disparate issues and injuries.

Strauss said he hoped other players might follow the Seau family's lead and opt out of the deal to force the two sides to negotiate a better deal.

"Ideally, our opt-out may cause others to consider that, and, in the ideal world, would cause the league and the plaintiffs [lead attorneys] to perhaps re-examine the settlement so they come up with something that addresses the claims of all those in the [lawsuit] and not just the few," Strauss said.

It is unclear how many other players, if any, have signaled their intent to oppose the deal. Strauss said the Seau family will formally notify an administrator of its intent to opt out before an Oct. 14 deadline. Players also have until that deadline to formally object to the deal. A large number of opt-outs could become a factor in the judge's decision to give final approval.

It's also not clear how -- and when -- Seau's case would be allowed to proceed back in California Superior Court in San Diego. It first needs to be remanded back to that court by Judge Anita Brody, who is overseeing the mass case, which conceivably could be held up for years in appeals.

"That's another problem; our case could be held hostage by the settlement," Strauss said. "We're opting out, but also want to proceed, want to be able to get on with the case."

Seau, who was 43, shot himself in the chest with a .357 Magnum revolver following years in which his family and friends noticed marked changes in his behavior. Previously a responsible and loving father, Seau lost control of his finances, gambled excessively and became disconnected from his relatives, including his children.

Shortly after his death, the NFL intervened in an unseemly battle among neuroscientists who wanted to study his brain. Members of the NFL's concussion committee helped direct the brain to the National Institutes of Health, where five separate neuroscientists found signs of the destructive neurofibrillary tangles that cause CTE.

Seau's case might pose a larger threat to the NFL than any other player suing the league. In addition to his name recognition and popularity, his medical record and clinical history are well-documented. In addition, his career coincided with an era in which the NFL's own research arm, created by former commissioner Paul Tagliabue, denied repeatedly in scientific articles and public statements that NFL players are susceptible to brain damage.

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That committee, led by Tagliabue's personal physician, Elliot Pellman, who was also the New York Jets' team doctor, attacked neuroscientists who presented evidence suggesting that, in fact, the repeated head trauma related to football had led to significant brain damage in an alarming number of former players, including Hall of Fame Pittsburgh Steelers center Mike Webster and Chicago Bears defensive back Dave Duerson.

Duerson's relatives also sued the NFL. They have not yet indicated whether they intend to opt out of the deal.

Duerson's lawyers also have complained about the unwillingness of the NFL and lead counsel for the players to share information about how the settlement was reached and how the grid designating payoffs for various cognitive issues was crafted. In response to motions by entities such as ESPN, Bloomberg and several players, the league and the lead counsel for the plaintiffs signaled this week that they will produce the documents if the judge orders them to do so.

"We'd like all the info, we can't determine how the grid was even determined," Strauss said. "How did they come up with the grid amounts? We'd like to know the foundational basis that was presented to ... the court for approval. There has been a real sound of secrecy around these settlement discussions and the whole process."

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New Concussion Settlement a Win-Win

June 26, 2014 by Andy DeGory

A new proposed settlement in the NFL concussion litigation should alleviate many worries when it comes to compensation for players affected by brain injuries. The revised agreement removes the cap on the NFL's obligations to the monetary award fund, and guarantees that any retired player who develops a qualifying neurocognitive condition will receive compensation. Ultimately, it looks like a win-win for the NFL and the players.

In a Wednesday conference call, Chris Seeger, co-lead counsel for the retired NFL players, said the plaintiffs' counsel team had been confident that the \$765 million initially agreed upon last August would have been enough to cover the 65-year lifespan of the fund. They were supported by actuarial estimates from both parties. However, concerns over the fund's long-term future arose from both the court and the players.

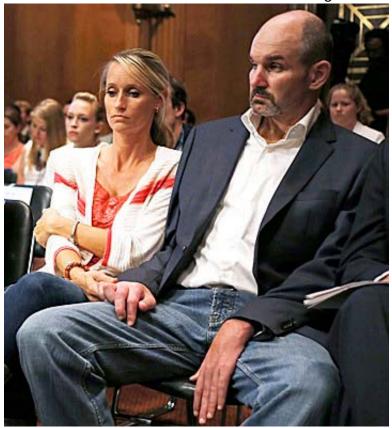
"We heard concerns from players who needed to trust that the money would be there in, say, 40 years," Seeger said.

U.S. District Judge Anita B. Brody denied the motion for preliminary approval for the settlement in January. After six months of work under the supervision of Brody and the court's special master, Perry Golkin, the agreement was reached to uncap the fund and fully guarantee that retired players would receive the necessary benefits during the 65-year plan.

In regards to the actuarial estimates that led to the initial \$765 million agreement, Seeger stated that those are now irrelevant due to the removal of the fund's cap.

"There is no scenario where a player won't get paid," said Seeger. "The biggest news of this is that in 15 or 25 years, you are still guaranteed to be compensated."

According to Seeger, aside from tightening some details the agreement between the players and the league remains largely unchanged. The standard will remain the same for players seeking benefits; severe



The compensation of Kevin Turner, a class representative in the suit who suffers from ALS, will not change. (Charles Dharapak/AP)

cognitive impairment will need to be proven to receive benefits. If, during a baseline assessment, mild cognitive issues are identified, players will be eligible for follow-up treatment as part of the program.

The monetary grid and scale to determine a player's compensation will remain unchanged as well. Seeger said that the plaintiffs never thought of trying to change the grid or its pay values during the revision of the settlement.

One change of note is that the NFL's ability to appeal claims is now unlimited, whereas they were limited to 10 appeals a year in the July agreement. Some argue that this could give the league a loophole to minimize claims.

Kevin Turner, a former Eagles and Patriots fullback, <u>now suffers from ALS</u>. A class representative in the lawsuit, his compensation ceiling of \$5 million will not change with the new agreement. Turner's statement:

"The compensation provided in this settlement will lift a heavy burden off of the men who are suffering," Turner said in a statement. "I am also personally comforted by the knowledge that this settlement is guaranteed to be there for any retired player who needs it. This settlement is another important step for ensuring that future generations of football players do not suffer the way that many in my generation have."

It appears as though both sides got it right on the second iteration. The uncapping of the fund ensures the effectiveness of the compensation program. It alleviates concern over the long-term viability of the initial \$765-million agreement, and expedites the process for players who are in need right now.

There is no scenario where a player won't get paid," said Seeger. "In 15 or 25 years, you are still guaranteed to be compensated.

Judge Brody and Special Master Golkin deserve credit for working through the initial settlement and ultimately ensuring that the appropriate compensation was allocated. Brody's decision to reject the first settlement looks like it was the right move.

During the conference call, Seeger used the phrase "100% guarantee" multiple times when addressing players' ability to receive benefits. The NFL and the retired players have to be pleased on two fronts: Once the settlement is approved, the compensation program will come into effect soon and start providing benefits to players in need; and recent retirees who could be affected in the future now know that the coverage will be there.



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NFL reaches concussion settlement

Gary Mihoces, USA TODAY Sports

7:08 p.m. EDT August 29, 2013



(Photo: Evan Habeeb, USA TODAY

The NFL and more than 4,500 former players want to resolve concussion-related lawsuits with a \$765 million settlement that would fund medical exams, concussion-related compensation and medical research, a federal judge said Thursday.

MORE: The judge's order (http://i.usatoday.net/sports/nfl/2013-08-29-NFL-Concussion-Litigation-Settlement.pdf)

Q&A: What this means (http://www.usatoday.com/story/sports/nfl/2013/08/29/nfl-concussion-lawsuit-settlement-judge-layn-phillips/2727589/)

The plaintiffs include at least 10 members of the Pro Football Hall of Fame, including former Dallas Cowboys running back Tony Dorsett. They also include Super Bowl-winning quarterback Jim McMahon and the family of Pro Bowl linebacker Junior Seau, who committed suicide last year.

BELL: Right time for settlement (http://www.usatoday.com/story/sports/nfl/columnist/bell/2013/08/29/nfl-bell-concussion-lawsuit/2729447/)

HEADS UP: Can game be made safer for kids? (http://www.usatoday.com/story/sports/nfl/2013/08/27/heads-up-youth-football-nfl-roger-goodell/2711317/)

Senior U.S. District Judge Anita Brody in Philadelphia announced the proposed settlement Thursday after months of court-ordered mediation. She still must approve it at a later date.

Former NFL fullback Kevin Turner, who suffers from ALS, also known as Lou Gehrig's Disease, spoke in a halting voice during a teleconference Thursday as he welcomed the settlement.

"It's been a struggle to get to this point, but today ... I am very proud that the NFL has decided to stand up for all the former players who are suffering from brain injuries," said Turner, 44, who played with the Philadelphia Eagles and New England Patriots and was a plaintiff in the suits.

"You know it's easy to forget just how many men have played in the NFL throughout the years. That's why today is so important for those who are hurting. This will bring help for them.

He added: "The compensation provided in this settlement will lift the huge burden off the men who are suffering right now, both them and their and families. It will give them the peace of mind to have the best quality of life they are able to have. They'll no longer have to make decisions regarding their health based on what they can afford."

Although some might see the settlement as low, the case was complicated and not a slam-dunk for the ex-players. Meanwhile, the NFL was battling a public relations nightmare of appearing to be a bully for even fighting the case.

Players attorney Christopher Seeger acknowledged there would have been risks in litigation. The lawsuits might have been dismissed.



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USA TODAY Sports' Jarrett Bell analyzes the \$765 million settlement.

"This is the only program where everybody get justice. ... Everybody wins," Seeger said.

He said all retired players, not just those who sued, will be eligible for a brain assessment program, and those found to have a certain level of impairment will receive a medical benefit card that be used for further testing and treatment.

Seeger said players who develop problems such as ALS, Alzheimer's or severe dementia will receive a benefit, in some cases as high as \$5 million. He also said the families of players who committed suicide will be eligible for "a seven-figure payout."

Seeger said former players will not have to prove their brain conditions are linked to NFL concussions.

"You don't have to prove that your neurological problem is related to a concussion. You don't have to prove in the settlement that you sustained a concussion in the NFL," Seeger said. "You just need to be a former retired player and you're in the program."

Many former players with neurological conditions believe their problems stem from on-field concussions. The lawsuits accused the league of hiding known risks of concussions for decades to return players to games and protect its image.

The NFL has denied any wrongdoing and has insisted that safety has always been a top priority.

A BETTER HELMET: Or just wishful thinking? (http://m.usatoday.com/article/sports/2601063)

DATA: Concussions keep players out longer (http://www.usatoday.com/story/sports/nfl/2013/07/31/concussions-keeping-nfl-players-off-the-field-longer/2604023/)

The settlement likely means the NFL won't have to disclose internal files about what it knew and when, about concussion-linked brain problems. Lawyers had been eager to learn, for instance, about the workings of the league's Mild Traumatic Brain Injury Committee, which was led for more than a decade by a rheumatologist.

In court arguments in April, NFL lawyer Paul Clement asked Brody to dismiss the lawsuits and send them to arbitration under terms of the players' contract. He said that individual teams bear the chief responsibility for health and safety under the collective bargaining agreement, along with the players' union and the players themselves.

One players lawyer, David Frederick, accused the league of concealing studies linking concussions to neurological problems for decades. But Seeger took the money over a peek into the NFL's files through discovery.

"It's always my preference not to continue to drag the litigation into a settlement process. It's not productive," Seeger said. "We made some pretty serious allegations in our complaint. But when we got into a point where we were looking to settle the case, I put that aside and only had one goal in negotiating and that was achieving the right result for players."

He said the primary goal was "substantial payouts" for severely injured players and testing and care for the others.

"I know many people would have been interested in seeing everything in the NFL's files, but at this point because we achieved the result we achieved and the NFL stepped up and settled the case, it's not a big concern for me. We got what we wanted."

MORE: Former QB Rypien applauds settlement (http://www.usatoday.com/story/sports/nhl/2013/08/29/former-washington-redskins-quarterback-mark-rypien-nfl-concussion-settlement/2728781/)

Brody had initially planned to rule in July, but then delayed her ruling and ordered the two sides to meet to decide which plaintiffs, if any, had the right to sue. She also issued a gag order, so it has been unclear in recent weeks whether any progress was being made.

The lawyers were due to report back to her Tuesday, but Brody instead announced in court files Thursday that the case had settled.

In recent years, a string of former NFL players and other concussed athletes have been diagnosed after their deaths with chronic traumatic encephalopathy, or CTE. Those ex-players included Seau and lead plaintiff Ray Easterling, who filed the first suit in Philadelphia in August 2011 but later committed suicide.

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About one-third of the league's 12,000 former players have joined the litigation since 20 m. They include a few hundred "gap" players, who played during years when there was no labor contract in place, and were therefore considered likely to win the right to sue.

In their suits, the former players allege that for decades the NFL knowingly failed to protect players from concussions. The suits allege long-term effects such as depression, dementia and suicide, such as the 2012 death of Seau and the 2011 suicide of former Chicago Bears great Dave Duerson.

More than 200 suits filed across the country against the NFL by ex-players were consolidated in Philadelphia. Brody had been expected to rule July 22 on an NFL motion to dismiss the suits. The league argued that because the players were covered by collective bargaining agreements, the matter should be settled by arbitration.

Brody ordered the mediation after what she described as an "exploratory" telephone conference with the attorneys for both sides.

"I order parties, through their lead counsel, to engage in mediation to determine if consensual resolution is possible," she wrote.

Brody appointed Layn Phillips, a retired federal judge, as mediator. Brody ordered Phillips to report to her by Sept. 3 on the results of the mediation and said she would not rule on the NFL's motion to dismiss until then.

The two sides responded with brief statements saying they would comply with the order and make no further comment.

Contributing: The Associated Press

PHOTOS: Concussions and the NFL



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Is the 'Patriot Way' still working?



SPORTS ON EARTH



PATRICK HRUBY

July 18, 2014

CUTTING THEM SHORT



Former NFL linebacker Junior Seau was diagnosed with CTE posthumously. In one study, 33 of 34 football players tested positive for the disease. (Getty Images)

Dave Pear was still alive. Potentially, this was a problem. It was the day after a federal judge had granted preliminary approval of a proposed settlement of a class action brain damage lawsuit brought by retired players against the National Football League, and Pear was on the phone with me, trying to make sense of the deal. What kind of illness and injury did it cover? How much money could suffering retirees expect? Why did the agreement make all sorts of seemingly arbitrary, non-medical distinctions, like one between different degrees of dementia?

Pear didn't know. He said his lawyer didn't know, either. A 61-year-old former Pro Bowl defensive tackle now afflicted by a variety of football-induced maladies -- vertigo, memory loss, constant physical pain following multiple neck, back and hip surgeries -- Pear already had spent years fighting to receive benefits from the NFL's much-maligned disability system, a treacherous legal and medical thicket that many retirees insist has been designed to cut costs by denying claims. He hoped the proposed settlement was different. That it would help everyone in need, every broken family and battered brain. Including his own.

"Is it a good deal?" Pear said. "It only covers certain people at certain times. Based on what I've read, you won't get compensation for CTE [chronic traumatic encephalopathy] until after you're dead."

Not exactly, I told him. To receive cash awards for CTE, a neurodegenerative disease that currently only can be diagnosed posthumously, former players must have died by a specific cutoff date.

"Well, what's the date?" Pear said.

Yesterday, I said.

Silence.

"That's horrible," Pear said. "That stinks. Unbelievable."

Believe it: According to the terms of the proposed settlement, NFL retirees may receive awards of up to \$4 million for "Death with CTE." but only if they've died between Jan. 1, 2006 and July 7, 2014. Anyone who died earlier is shut out. As is anyone reading this. Forever, Never mind that CTE -- a condition found in contact sport athletes, military personnel exposed to explosive blasts and others subjected to repetitive concussive and subconcussive head trauma, marked by widespread, irreversible accumulation of destructive tau protein in the brain -- is at the heart of the lawsuits against the league. That it's the disease of Junior Seau and Dave Duerson, Andre Waters and Justin Strzelczyk. That it's the deus ex machina of "League of Denial," a malady that the NFL's handpicked, under-qualified, since-discredited concussion doctors insisted neither existed nor could be linked to football, all while the neuropathologist who first discovered CTE's telltale tau tangles in Hall of Fame center Mike Webster's brain, Bennet Omalu, considered calling it footballer's dementia.

Never mind, too, that the proposed settlement does not assign similar cutoff dates to former players diagnosed with amyotrophic lateral sclerosis (Lou Gehrig's disease), Alzheimer's or Parkinson's -- even though a 2013 National Institute for Occupational Safety and Health study of nearly 3,500 NFL retirees who played at least five seasons between 1959 and 1988 recorded just 17 combined cases of the aforementioned diseases, while 33 of the 34 deceased NFL players in a 2010 study were diagnosed with CTE. This left neuropathologist Ann McKee to wonder whether "every single football player doesn't have" it.

"[The cutoff] is one of those things that when you say it out loud, it just sounds ridiculous," says Alan Faneca, a former NFL lineman and one of seven retirees who have filed an objection to the proposed settlement. "It sounds crazy. To have such a small window -- the guys like Mike Webster who helped build and create the game having passed away before and their kids and families don't get anything, and the current guys who luckily enough lived past Fourth of July weekend not getting anything either? It doesn't make sense. It's a line drawn in the sand, entirely not on the right place."

A lawyer who requested anonymity because of his ongoing work on football brain damage litigation is more blunt. Picture the settlement's upcoming fairness hearing, he says, currently scheduled for November, in which Judge Anita Brody must listen to objections and concerns 1A3415

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How the NFL's concussion settlement cuts coverage. I sportson Earth com: Patrick Hruby Article

before giving the deal final approval. Now picture Omalu or McKee standing in a federal courtroom in Philadelphia, holding aloft two jars.

In Jar No. 1: The brain of an NFL retiree who died before July 7.

In Jar No. 2: The brain of a retiree who died afterward.

"Just imagine [them saying], 'both show significant signs of brain damage, yet only this one is entitled to \$4 million," the lawyer says.

"'Preposterous, your honor.""

* * *

Preposterous? Not at all. More like a simple misunderstanding. At least according to Chris Seeger, the co-lead attorney for the players on the proposed settlement. Two nights after I spoke with Pear, Seeger was a guest on CBS Sports radio. He wanted to, in his words, "straighten this out." (Full disclosure: Seeger specifically wanted to straighten *me* out -- the previous evening, <u>I had been a guest on the same show</u>, and had criticized both the death with CTE cutoff date and other aspects of the settlement).

"You know, frankly, we didn't care if you have CTE or not," Seeger said.

The settlement, Seeger explained, wasn't set up to help NFL retirees with CTE. It was set up to help retirees who are sick. Sick enough to show symptoms of neurodegenerative disease. The deal awards cash payments to former players who receive a "qualifying diagnosis" of ALS, Parkinson's, Alzheimer's or dementia. The first two conditions can be definitively diagnosed in the living. CTE cannot, Instead, a definitive diagnoses requires an autopsy, same as Alzheimer's and some types of dementia. A neuropathologist must cut a patient's brain into thin slices, stain them with chemical markers and examine the results under a microscope.

Rather than pay the families and estates of deceased ex-players who have been diagnosed with CTE, the settlement seeks to dispense money to retirees while they are still alive. How? In order to be eligible for a payout, former players must enroll in a Baseline Assessment Program, a neuropsychological testing program that screens for signs of cognitive impairment. If a retiree with CTE has enough impairment to qualify for dementia or Alzheimer's -- both of which have some symptoms which overlap with those of CTE -- he'll get his award in the here and now. Which means he won't need a death with CTE payout. Hence the cutoff date.

That's the logic, at least.

"I think people got really hung up on CTE, but, you know, this is all about symptoms," Seeger said on the radio. "If you're sick, and your activities of daily living are being interfered with, you can't function, you're going to get paid whether or not you have CTE."

This sounds reasonable. Unless you've read the scientific literature written by researchers who study CTE. Or have talked to family members of men who have succumbed to the disease. In which case, it sounds like a sneaky evasion. And also completely ludicrous. Despite Seeger's reassurances, the settlement not only figures to stiff-arm every current NFL retiree unfortunate enough to have CTE and die after July 7, but also many of those same retirees who have to *live* with the disease in the meantime. The very same symptomatic ex-players struggling with daily life who Seeger insists are covered by the deal.

Consider Lew Carpenter.

Carpenter was a football lifer. He played on the Green Bay Packers under Vince Lombardi. Coached in the NFL for 31 years. When he died from pulmonary fibrosis four years ago at age 78, Boston University researchers studying CTE called his daughter Lisa's house. They had an unusual request. They wanted to examine Lew's brain. His family had never heard of the disease. They said *yes* anyway, knowing Lew would have wanted to help other players. Lew's other daughter, Rebecca, wasn't sure what to expect. Dad had taken plenty of hits as running back, receiver and defensive back, but never had been diagnosed with a concussion. Well into his 50s, he had remained mentally sharp -- sharp enough to serve as an assistant coach for eight different NFL teams, as well as sideline stints with the World League of American Football's Frankfurt Galaxy and Southwest Texas State University. Only in his final years did Lew seem obviously impaired: he had trouble finding the right words, remaining organized, remembering why he was going to the doctor.

Rebecca was at her home in Los Angeles when the call came from Boston. Your father had CTE. An advanced case. No signs of Alzheimer's or any other neurodegenerative diseases. She was sick to her stomach, Didn't believe it. Didn't know a thing about CTE, either. Thought it might JA3416

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be bullshit, a made-up disease, hyped by opportunistic lawyers and overeager scientists. Football was the greatest thing in her father's life, a sport that had lifted him out of childhood poverty, given him everything ... and *this* was what it had done to him? No. Just no. Even when Rebecca read the pathology report a few months later, she remained in denial. Until she saw the images of her father's brain, dotted with dark splotches of stained tau. "It was really shocking how much damage there was," she says. "On a scale of one to four, he was a four. Then I looked at the symptoms and was like, 'oh my god, that was a symptom. That was a symptom."

Suddenly, some of her father's inexplicable past behavior started to make sense. Like his mood swings. Like when someone would let the family's dogs into the house, and Dad would start screaming, totally spooked, as if someone had planted a live IED in the living room. *Goddamnit, who let the dogs in!* "He would call up and say, 'how is such and such,' and I would say, 'Dad, that was last year!' Rebecca says. "I would get mad and frustrated and think he doesn't care, he's not listening. But he had brain damage. And we didn't know. He was really high functioning in a lot of ways, but still had a lot of brain damage that impaired his ability to be in relationships and hold down jobs. You can look drunk, like under the influence of drugs. People don't know. It comes and goes. It's intermittent. It's crazy. It's like a frog in a pot of cold water and you slowly turn up the heat, and by the time they are boiling to death they don't even notice the change."

Rebecca talked to her mom, Ann, who first met Lew when she was 15.

Mom, when did it start to go south?

It was really in his 40s.

Among CTE case studies, Lew's story is hardly unique. Mood and behavioral problems often come first, followed by cognitive impairment. Duerson followed that path, his marriage ending, his business empire imploding, his dreams of becoming mayor of Chicago dashed, all before he began having blurred vision and headaches, memory loss and problems spelling common words. In 2011, he shot himself in the heart with a revolver, asking that his brain be donated to CTE researchers. Prior to committing suicide in 2012, Seau likely would not have been diagnosed with dementia or Alzheimer's. He was functional. Still there. Nevertheless, something had shifted, gone awry: He was womanizing, drinking heavily, gambling too much, acting impulsively, making bad financial decisions, hiding depression, forgetting things, having trouble sleeping.

Last year, Boston University CTE researcher Robert Stern and other scientists <u>published a study of 36 adult males who had the disease</u>. All were athletes. Twenty-nine played football. None suffered from any other neurodegenerative or motor neuron disease. Three were asymptomatic when they died. The rest were not. They fell into two clinically distinct groups, labeled "cognitive" and "behavior/mood." Each group was consistent with earlier case reports of CTE in boxers.

The first group consisted of 11 men. As patients, they suffered first from cognitive impairment -- memory problems, executive dysfunction. They tended to live longer, and their symptoms tended to show up later in life, typically in their late 50s. By contrast, the 22 men were in second group generally died younger, and their symptoms appeared earlier. Moreover, the symptoms themselves were totally different: Emotional explosiveness, impulsive behavior, outbursts of violence, depression and hopelessness.

When Duerson was 45 years old, he inexplicably threw his wife, Alicia, against a wall during an argument. She <u>later told Men's Journal</u> that he had never been violent before, and that his behavior came from "the changes" -- a new hair-trigger temper, sudden downshifts in mood and a lack of impulse control.

Back to the settlement. If you get sick, Seeger says, you get paid. This is all about symptoms. Is it? Is it about Duerson's "changes?" The following symptoms are associated with both brain damage and CTE: Sensitivity to noise, visual impairment, chronic pain, chronic headaches, numbness, burning, tingling, incessant ringing in the ears, attention disorders, trouble sleeping, aggression, agitation, impulsivity, suicidal thoughts and difficulty regulating, expressing and controlling complex emotions. None of these are covered by the settlement. Remember the Baseline Assessment Program? It screens for "sick." It defines "symptoms." It is the first tollbooth on the road to cash awards. As previously mentioned, it consists of neuropsychological tests used to detect cognitive impairment. Not mood and behavioral issues.

In other words, the proposed deal has been designed as if only the first group from the Stern CTE study matters. Meanwhile, members of group two -- the Duerson and Seau cohort, and quite possibly the bigger cohort -- will be ignored, not paid a dime, at least until they live and suffer long enough, like Carpenter, to join the first group in measurable cognitive decline. And even that isn't guaranteed: In one study of CTE, a quarter of the individuals diagnosed with Stage III of the disease -- CTE runs on a scale, with IV being the most advanced stage -- $\frac{1}{1}$

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were not considered cognitively impaired.

In the Stern study, only 10 of the 33 symptomatic subjects were ever diagnosed with dementia.

"I once happened to run into a social worker who helps rehabilitate former gang members," says Carpenter, who is working on a film about her father, My Dad's Brain, and has spent the last two years crisscrossing the country interviewing former football players and scientists to better understand how blunt force head trauma and neurodegenerative diseases can affect personality and behavior. "It turns out one of their first intake questions is, 'have you ever had a blow to a head?' They understand that a guy with that may need special intervention if they can help him at all, because that can have a major impact on your ability to regulate emotion and anger. Only that isn't covered by the settlement at all. That leaves me scratching my head."

"Stern says there are two types of CTE," says Gordon Johnson, a Wisconsin-based brain injury lawyer and advocate. "In this settlement, I don't know how you get compensated for the second type without having already killed yourself."

More head-scratching: Many scientists believe that there will be a way to detect CTE in the living within the next decade. This isn't blind faith in the march of progress, like expecting warp drives and flying cars. It's a pragmatic assumption, rooted in current research. Scientists in Chicago are experimenting with a screening test that measures vision, eye movement and optic nerve irregularities. Stern's team in Boston is currently conducting a comprehensive study of 100 NFL retirees, hoping to identify CTE biomarkers. Other researchers are developing and refining scanning technology to see tau deposits in the brain; just this week, scientists from Massachusetts General Hospital attending the Alzheimer's Association International Conference in Copenhagen announced a new type of brain imaging that can show tau tangles in living people for the first time.

Inexplicably, the settlement barely takes future scientific advances into account. While the deal covers the next 65 years, it specifically prohibits the NFL and the players' top lawyers from meeting more than once every 10 years to discuss possible changes to both the agreement's qualifying diagnoses and the protocols for making them, with actual modifications needing approval from both sides. (Translation: If the NFL doesn't want to accept a new method of detecting CTE, it doesn't have to). More significantly, any and all changes will not affect the bottom line. From Section 6.4 of the settlement, "Modification of Qualifying Diagnoses":

In no event will modifications be made to the Monetary Award levels in the Monetary Award Grid, except for inflation adjustment(s)

"CTE isn't just being written out here, it's being written out for three generations," Gordon says. "How stupid is this settlement going to look in 10 years if a brain scan can prove CTE, and we have 1,000 players with this disease, and they can't get an award, and there's nothing you can do in this agreement to change if they should get an award?"

The lawyer was incredulous. His clients were confused. He couldn't go on the record -- he represents a group of NFL retirees within the class action suit, and is still figuring how what to advise them in terms of objecting to the deal or opting out altogether -- but asked me to call, anyway.

He wanted to vent.

The lawyer had seen a set of brain scans. Three former players. One in his 30s, one in his 40s, one in his 70s. All still alive. The scans were experimental, provided by a scientist researching neurodegenerative disease. *You can see it,* the lawyer said. *You can see the CTE.*

"Why aren't these players entitled to that diagnostic advantage today -- or in the future?" he said. "Nothing in the settlement provides for that. This started out as a CTE case. It is a CTE case. You have 33 of 34 autopsies confirming CTE. And on top of that, if someone dies today and an autopsy is performed and CTE is found, their family gets nothing? That's not representing these players well. It's ridiculous."

In his interview with *The Sporting News*, Seeger said that he and co-counsel Sol Weiss specifically fought to make sure CTE was not used to determine eligibility for cash awards because: 1) they didn't want anyone to challenge players to have to prove they have it; 2) they didn't want players to have to prove that the disease was specifically related to concussions. This makes little sense. Medical experts can see CTE in the dead. They will be able to see it in the living. How much more proof is necessary? As for the link between football-induced brain damage and neurodegenerative disease, there is no definitive proof that the former causes the latter. Not yet. However, there is a growing JA3418

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<u>hody of suggestive</u>, <u>supportive evidence</u>. And given that evidence, no honest scientist would argue that getting hit in the head over and over is anything but had for one's brain.

In the case of CTE, the tau deposit patterns that identify the disease -- and distinguish it from, say, Alzheimer's -- have been found only in people who have endured repeated head hits or at least one battlefield blast injury. No brain insult? No CTE, according to McKee and other neuropathologists. On the other hand, while medical experts suspect that the other neurodegenerative diseases compensated by the settlement -- ALS, Parkinson's, Alzheimer's and dementia - may be triggered and/or accelerated by years of bashing helmets with opposing middle linebackers, those same illnesses also occur in people who haven't experienced brain trauma. The link to football is less clear.

By Seeger and Weiss' own logic, then, the settlement's award structure ought to prioritize CTE over other ailments. So what gives? Why are symptomatic former players being left high and dry? Why has the deal become the equivalent of an asbestos lawsuit settlement that severely restricts future mesothelioma claims?

The answers may lie in basic math.

When Seeger and the NFL first asked Judge Brody for preliminary settlement approval in January, the deal's award fund was capped at \$675 million, an amount that player and league attorneys both claimed was enough to cover 65 years' worth of potential claims from an estimated pool of 20,000 retirees. Brody disagreed, denying their motion. The NFL and Seeger resubmitted the settlement in June, this time "uncapping" the fund -- but still confidently claiming in court documents that total payments by the league over the agreement's lifetime would not exceed the original amount.

During his interview with CBS Sports radio, Seeger was asked by show host and former NFL linebacker Brian Jones how he arrived at \$675 million. Seeger said that he hired "the best economists and actuaries in the country, guys that do this kind of work." They looked at the rates of the neurodegenerative diseases covered by the settlement within the general population, compared those rates to every published study of the same diseases in NFL players, factored in football career length, and came up with an amount that Seeger was "extremely comfortable with."

"Sitting here right now, I'm still comfortable that those numbers are good," Seeger said.

"What percentage of the players," Jones said, "by your estimation, are going to receive compensation as a result of this settlement?"

"It could be as high as 3,000, 4,000, maybe 5,000 players at the end of the day, over the lifecycle of this agreement, will get cash compensation," Seeger said.

Headline: National Football League expects as many as 25 percent of its former players to develop devastating, diagnosable neurodegenerative diseases. Not the greatest endorsement for the sport. Putting that aside, however, let's do some arithmetic. Seeger estimates that between 3,000 and 5,000 former players will be compensated. By silent assent, the NFL concurs. Both parties insist that \$675 million is sufficient to pay those retirees off under the terms of the settlement. Perform long division, and that means the average expected award is between \$135,000 and \$225,000.

That's a far cry from the settlement's maximum \$5 million award for ALS. From its \$3.5 million max for Alzheimer's and Parkinson's. From its \$1.5-3 million max for dementia. Moreover, it isn't even close to the roughly \$10 million in total lifetime costs -- including lost productivity and medical and custodial care -- that University of Toronto neurosurgeon Charles Tator estimates for each and every case of repetitive traumatic brain injury.

Oh, and also, it's as much as 833 times smaller than a separate \$112.5 million that the NFL is required to pay Seeger, Weiss and four other attorneys within 60 days of the settlement receiving final judicial approval.

How do you get the NFL to sign off on a deal that theoretically exposes the league to uncapped, *unlimited* future financial liability? Easy. You make sure that said liability is, in fact, quite limited. <u>Under the terms of the settlement</u>:

• All cash awards are subject to reductions based on a grid that accounts for career length and retiree age at the time of receiving a qualifying diagnosis. Former players with fewer than five credited years of NFL experience will see their awards reduced, some by more than half. The same holds true for retirees over 45 -- the older players are when diagnosed, the less money they'll receive.

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- Any retiree who has suffered a single non-football related traumatic brain injury or stroke will have their award reduced by 75 percent, never mind that 1) there is no scientific reason to presume that a single non-football brain injury accounts for three-quarters of a player's afflictions; 2) NFL team doctors increased former players' risk of stroke (and likely, their risk of brain injury) by administering the painkilling drug Toradol.
- Retirees do not receive credited seasons for playing in NFL Europe, even though time spent on "practice, developmental, or taxi squad[s]," is credited, and the laws of physics and biology with regards to collisions and concussions still apply on the other side of the Atlantic Ocean.
- The settlement's diagnostic program and claims process is rife with potential pitfalls that could make it difficult for a completely healthy person to receive an award, never mind a brain-damaged former player with cognitive or emotional challenges. Example No. 1: Retirees who fail to register with the settlement within 180 days of a supplemental notice being distributed are totally ineligible for benefits, as are players over age 43 who fail to get a Baseline Assessment Program exam within two years. Meanwhile, some of the ex-players who most need help are indigent. Example No. 2: The NFL is allowed to make unlimited appeals of player claims, and players must pay a \$1,000 fee to contest them. Example No. 3: BAP program neuropsychologists cannot make qualifying diagnoses of Alzheimer's, Parkinson's or ALS; instead, retirees must visit a settlement-approved doctor and pay for both their medical testing and related travel expenses themselves.

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Similarly, the settlement's restrictions on CTE seems designed to cut the NFL's costs. The grid reduces the size of individual death with CTE payouts, while the cutoff date limits the total number. In disallowing future award changes regardless of medical advances -- in essence, the potential creation of a "Life with CTE" qualifying diagnosis -- the settlement shrinks the eligible player pool even further, same as pretending NFL Europe hits to the head don't count. By exclusively focusing on cognitive impairment, the same BAP program that is supposed to assist CTE sufferers by giving them a general dementia diagnosis actually *forecloses* on retirees who are suffering from mood, behavioral and other non-cognitive symptoms like chronic migraines -- all while saving the league money by ensuring that living explayers with CTE who *do* manage to qualify for a dementia award are more likely to be older, and therefore subject to a greater payout reduction according to the aforementioned offset grid.

Think back to that NIOSH study. Almost 3,500 NFL retirees. Just 17 cases of Parkinson's, Alzheimer's and ALS over a 29-year-span. By contrast, neuropathologists have been looking in earnest for CTE in the brains of former football players for less than a decade -- and since they've started, they've mostly found it. If you were a league lawyer or negotiator working on the settlement, which of those diseases would you most try to write out of a deal?

"[The settlement] is a money grab," Faneca says. "A money grab by lawyers trying to get paid and get out. And by the NFL trying to keep this is as small as possible. Of course the league would agree to an unlimited number, because the window is still so small in terms of neurological disorders they agree to cover compared to the broad stroke of things."

Eleanor Perfetto has a related problem with the settlement. Her husband, Ralph Wenzel, played in the NFL. After a slow, painful, JA3420

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emotionally agonizing physical and mental decline, Ralph died in 2012 at the age of 69. He was posthumously diagnosed with Alzheimer's and CTE -- but originally diagnosed with early dementia in 1999.

During his first visit with a neurologist, Ralph was asked when he first began to have trouble remembering things. He told the story of a 1994 high school football practice, where he bean to teach his linemen a new blocking technique.

Hey, coach, you taught us that yesterday.

10/1/2014

Ralph was dubious. He asked his players to explain the technique in question. They did so perfectly, precisely the way he planned to teach it. Because he *had* taught it. Only he didn't recall doing so. That same year, the NFL formed its Mild Traumatic Brain Injury Committee -- a group that spent more than a decade producing junk science, denying and downplaying links between football and brain damage, between concussions and long-term neurological harm. A group whose discredited work and dangerous medical recommendations are at the core of the lawsuits that have produced the proposed settlement.

"With many of the older [NFL retirees], the date of their formal diagnoses is probably many years after they became sick," says Perfetto, a University of Maryland professor specializing in health policy and epidemiology, and a plaintiff in the lawsuits against the league. "So like Ralph, maybe they had symptoms for five or 10 years before a formal diagnosis. And one of the reasons they didn't realize they needed to get checked out, or did get checked out but doctors couldn't figure out what was wrong with them, was all of the efforts the NFL made to smokescreen that this problem didn't exist. Which is exactly what plaintiffs are suing for."

Back to the settlement's award grid. Perfetto says her attorney told her that her husband is due a \$1.4 million payout for his postmortem diagnosis of CTE, based on his official dementia diagnosis at age 56. Had he instead been diagnosed in 1994, his award would have been closer to \$3 million. Or consider a widow Perfetto knows, a woman in her 80s. She cared for her sick husband, a former NFL player, for more than 30 years. Behavior problems began in his early 50s. Cognitive impairment emerged in his 60s. Confused doctors misdiagnosed him with bipolar disorder and other illnesses, and only diagnosed him with dementia when he was nearing 70.

The man died in his early 80s. Researchers found CTE in his brain. Thanks to the grid and her husband's late age of formal dementia diagnosis, the widow is due to receive \$600,000 -- millions less than the league would be required to pay out had the man's mood and behavioral symptoms counted toward a qualifying diagnosis, and a scenario that figures to be repeated if the current settlement proposal receives final approval.

"This is the one thing that bothers me a lot," Perfetto says. "The NFL has actually managed to reward themselves for their deceit."

* * *

Tony Dorsett had no idea. For that matter, neither did Brad Townsend. It was late afternoon on the day that Brody had granted the settlement preliminary approval, and Townsend, a reporter with the *Dallas Morning News*, had called the Hall of Fame running back for his reaction.

"It was the right decision," Dorsett told Townsend.

Now 60, Dorsett is a plaintiff in the brain-damage lawsuits. He also is struggling. Last year, he was diagnosed by doctors at the University of California, Los Angeles as having signs of CTE. Townsend had talked to Dorsett over the phone last August, and again in November. His ability to hold a steady train of thought seemed to have deteriorated. Nevertheless, he told Townsend that he didn't know the size of the award that he might receive from the settlement, and that perhaps it didn't much matter.

"My brain is priceless," Dorsett said. "There isn't enough money that they can give me to make me want to look the other way."

When I saw <u>Townsend's subsequent article</u>, I sent him an email. Did Dorsett realize that the only way for him to receive a CTE award from the settlement was to have dropped dead the previous night?

Townsend wrote back. He said he would give Dorsett another call. The next day, he sent me a follow-up note:

... I spoke to Dorsett. He said he frequently communicates with his attarney and this is the first he's heard of a CTE loophole ... He said he was 1A3421

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"going to get all over this" and call his attorney ...

Dorsett wasn't alone in missing the settlement's death with CTE award cutoff date. An Associated Press story on Brody's preliminary approval didn't make note of it. Neither did a piece in the *Minneapolis Star-Tribune*. The first page of a proposed long form settlement notice that will be sent to NFL retirees doesn't mention it specifically -- instead vaguely stating that the deal will provide "monetary awards" for "certain cases of CTE" that are "diagnosed after death" -- while a YouTube video supporting the settlement aimed at former players and produced by plaintiff's lawyers doesn't mention it at all.



In a way, Faneca says, he can understand not knowing. Not wanting to know. Ignoring the fine print. Even though the objection to the settlement filed by him and six other former NFL players in late June takes issue with many aspects of the settlement, including the cutoff date.

"[Neurological problems] are definitely not something you like to think about, especially for you own family or families of your friends and people you know," he says. "You first instinct is denial. You think, 'it's not going to happen to me.' It's not a fun conversation with your wife.

"But the likelihood, as we now know it, is that there is a more than strong chance that I'm going to know somebody who is going to be going through these issues in some form or fashion. Guys will be needing help, and we need to broaden the scope of the settlement, open it up and get more guys covered."

And how do you do that?

"Right now, there's tons of guys who have no idea what is going on," Faneca says. "I have guys contacting me, asking to be informed. The settlement is a little daunting to comprehend, the ins and outs and all the exclusions. Who wants to read that stuff? But sometimes you have to suck it up and start handling it."

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Friday, September 12, 2014

Brain impairment begins younger

By Steve Fainaru and Mark Fainaru-Wada ESPN.com

NFL players are likely to suffer chronic brain injury at a "significantly higher" rate than the general population and also show neurocognitive impairment at a much younger age, according to documents filed on behalf of the league in federal court Friday.

Former players between 50 and 59 years old develop Alzheimer's disease and dementia at rates 14 to 23 times higher than the general population of the same age range, according to the documents. The rates for players between 60-64 are as much as 35 times the rate of the general population, the documents reported.

The figures, compiled by actuarials hired by the NFL, appeared to be the first public admission by the league that retired players incur brain damage more frequently than the general public. The report did not specify why the rates for retired players are significantly higher.

The NFL's report, along with one filed by the plaintiffs, was prepared for U.S. District Judge Anita B. Brody, who is presiding over the lawsuit in Philadelphia that accuses the NFL of hiding information that linked concussions to brain injuries. Brody sought the documents as evidence that a settlement the two sides reached in the case is sound.

"These results validate that our assumptions are reasonable and conservative because when compared to prevalence rates among the general population, they are significantly higher," wrote The Segal Group in the documents prepared for and presented by the NFL. "Moreover, as anticipated, the model determines that players will first be diagnosed with qualifying diagnoses at a younger age than the general population, which is consistent with plaintiffs' allegations."

Nearly three in 10 former NFL players will develop at least moderate neurocognitive problems and qualify for payments under the proposed concussion settlement, according to documents filed by the league and the players.

The Segal Group estimates that 3,488 former players will make nearly 6,700 claims for payments related to brain injuries caused by playing football, according to the documents. Of those 3,488 claims, 94 percent would be for Alzheimer's, Parkinson's disease or moderate dementia, but the NFL's documents show that many, if not the majority of, players will be ineligible for compensation before reaching age 80.

The settlement has come under intense criticism from several lawyers involved in the case, although it remains unclear whether that opposition could derail it. For months, many of those attorneys have been requesting the underlying actuarial data that negotiators relied upon to close the deal.

After reviewing the documents, one prominent lawyer who represents several former players said the data refuted the claims of lead negotiators that the settlement provides adequate compensation for players with chronic brain damage.

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"They're going around saying what a great settlement it is, when the average Parkinson's player gets \$320,000; that's utter nonsense," said the lawyer, who asked not to be identified for fear of upsetting Brody. "The average Alzheimer's guy gets \$340,000. That's just utter nonsense."

The players' actuary estimated that former players were at twice the risk for Alzheimer's, Parkinson's, Lou Gehrig's disease and dementia as the general population between the ages of 20-60 years old. After that, they estimated the ex-players' risk would be closer to normal.

The NFL's actuary reported significantly higher rates of Alzheimer's and dementia for all age groups. Players younger than 50 were at least eight times more likely to develop those diseases, for example.

In 2009, the NFL funded a University of Michigan study that showed that former players between 30-49 were 19 times more likely to have Alzheimer's and other mental disorders than men of the same age. But the lengue disorders than men of the same age. But the lengue disorders than men of the same age.



Roger Goodell and the NFL agreed this summer to pay out more than the \$675 million for player awards agreed to in the concussion settlement.

disorders than men of the same age. But the league disavowed the study, saying that it did not specifically study dementia and was based on unreliable phone surveys.

The documents released Friday have been sought for months by attorneys and media to understand how negotiators arrived at the settlement. The two sides announced in August 2013 that the NFL would pay \$765 million -- \$675 million designated to retired players with neurological impairment.

One actuary who reviewed both reports for ESPN said he was struck by how similar the findings were.

"It is common to have experts employed by each side wind up with substantially different conclusions," said Scott Witt, owner of Witt Actuarials and a frequent expert in damage calculations. "In this case, I was struck that both experts' reports are fairly harmonious."

Numerous retired players and attorneys have questioned whether the money was sufficient to cover the growing number of players with confirmed brain damage. At the time the proposed settlement was first announced, Christopher Seeger, a lead co-counsel who negotiated the deal for the players, promised that "analysis from economists, actuaries and medical experts" would prove that the settlement will cover "all eligible retired players."

But Seeger and the NFL refused to produce the information. Some attorneys speculated that the NFL was withholding the data because it contained potentially damaging information: the league's own estimates of how many players are likely to suffer brain damage.

That information goes to the heart of questions about the long-term health effects of tackle football. Despite mounting evidence about the link between football and brain damage, scientists have not yet established the prevalence of diseases such as chronic traumatic encephalopathy, or CTE, which has been discovered in dozens of NFL players following their deaths.

In January, Brody refused to provide preliminary approval for the deal. She ordered negotiators to turn over all documentation used to support the settlement, including the analysis by actuaries and economists, noting her concerns that not all qualifying players would be paid.

The plan would pay up to \$5 million for players with amyotrophic lateral sclerosis, also known as Lou Gehrig's disease; \$4 million for deaths involving CTE; \$3.5 million for Alzheimer's disease; and \$3

10/1/2014 Casea**18-2012**md**Document** 0**531133165800**44**Pages 550/90Da**te **Filed**: **208/09/2019** million for moderate dementia and other neurocognitive problems.

However, only men younger than 45 who spent at least five years in the league would get those maximum payouts. The awards are reduced, on a sliding scale, if they played fewer years or were diagnosed at a more advanced age.

The players' data therefore predicts the average payouts, in today's dollars, to be \$2.1 million for ALS, \$1.4 million for a death involving CTE, and \$190,000 for Alzheimer's disease or moderate dementia. The average ex-player being diagnosed with moderate dementia is expected to be 77 with four years in the NFL.

About 28 percent of all retired players are expected to be diagnosed with a neurocognitive injury that is eligible for compensation under the plan. But only 60 percent of them are expected to seek awards, based on prior class-action litigation.

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NFL

NFL: Nearly Three in 10 Ex-Players Will Develop Debilitating Brain Conditions

League Makes Disclosure As Part of Proposed Settlement of Concussion Suits

Associated Press

Sept. 12, 2014 9:32 p.m. ET

PHILADELPHIA—The NFL estimates that nearly three in 10 former players will develop debilitating brain conditions, and that they will be stricken earlier and at least twice as often as the general population.

The disclosure Friday comes in separate actuarial data the league and players' lawyers released as part of their proposed \$765 million settlement of thousands of concussion lawsuits.

Both the league and lead players' lawyers expect about 6,000 of the 19,400 retired players, or 28%, to develop Alzheimer's disease or at least moderate dementia. Dozens more will be diagnosed with Lou Gehrig's or Parkinson's disease during their lives, according to the data.

The reports were prepared for Senior U.S. District Judge Anita B. Brody, who is presiding over the class-action lawsuit in Philadelphia that accuses the NFL of hiding information that linked concussions to brain injuries.

The NFL report said the ex-players' diagnosis rates would be "materially higher than those expected in the general population" and would come at "notably younger ages."

The proposed settlement includes \$675 million for player awards, \$75 million for baseline assessments, \$10 million for research and \$5 million for public notice. It wouldn't cover current players.

Both sides have insisted that \$675 million would be enough to cover awards for 21,000 former players, given fund earnings estimated at 4.5 % annually. Ms. Brody initially had concerns the money might run out, while critics complained the NFL's offering is a pittance given its \$10 billion in annual revenues.

The NFL, in its report, said its estimates were "reasonable and conservative," and erred on the side of "overstating the number of players who will develop (illnesses)" to ensure the fund would be sufficient.

The league agreed this summer to remove the cap on its contributions, saying it would pay out more than \$675 million if needed, and pay more over time if needed. Ms. Brody then granted preliminary approval of the plan and scheduled a fairness hearing on the proposed settlement for Nov. 19, when critics can challenge it.

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"This report paints a startling picture of how prevalent neurocognitive diseases are among retired NFL players," lead player lawyers Christopher Seeger and Sol Weiss said in a statement.

Lawyers for some players have complained that the negotiations have been cloaked in secrecy, leaving them unsure of whether their clients should participate or opt out.

With an Oct. 14 deadline looming, "we still lack 'an informed understanding of the dynamics of the settlement discussions and negotiations.' Indeed, we have zippo understanding," lawyer Thomas A. Demetrio, who represents the family of Dave Duerson, wrote in a motion Thursday. Mr. Duerson, the popular Chicago Bears safety, committed suicide in 2011.

The family of former linebacker Junior Seau, who also committed suicide, has announced plans to opt out. He and Mr. Duerson are among about 60 former players diagnosed after their deaths with the brain decay known as chronic traumatic encephalopathy. Known as CTE, it can only be diagnosed after death.

Friday's release of the actuarial data was designed to address some of the complaints.

Critics also lament that the settlement plan offers no awards to anyone diagnosed with CTE in the future, and that the Alzheimer's and dementia awards are cut by 75 % for players who also suffered strokes.

The plan would pay up to \$5 million for players with amyotrophic lateral sclerosis, also known as Lou Gehrig's disease; \$4 million for deaths involving CTE; \$3.5 million for Alzheimer's disease; and \$3 million for moderate dementia and other neurocognitive problems.

However, only men under 45 who spent at least five years in the league would get those maximum payouts. The awards are reduced, on a sliding scale, if they played fewer years or were diagnosed later in life.

The players' data therefore predicts the average payouts, in today's dollars, to be \$2.1 million for ALS, \$1.4 million for a death involving CTE, and \$190,000 for Alzheimer's disease or moderate dementia. The average ex-player being diagnosed with moderate dementia is expected to be 77 with four years in the NFL.

Only 60% of those eligible for awards are expected to enter the program, based on prior class-action litigation. The payouts would top \$900 million, adjusted for inflation.

The 21,000 class members also include the estates of 1,700 deceased players.

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NFL: 3 in 10 ex-players face Alzheimer's, dementia

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Tight end John Carlson #89 of the Seattle Seahawks is carted off the field after an apparent head injury in the first quarter against the Chicago Bears in the 2011 NFC divisional playoff game at Soldier Field on January 16, 2011 in Chicago, Illinois. (Photo by Jonathan Daniel/Getty Images)

MARYCLAIRE DALE, The Associated Press

POSTED: Friday, September 12, 2014, 3:50 PM

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NFL: Nearly 3 In 10 Ex-Players Will Face Alzheimer's, Dementia Or Other Neurological Problems

AP | By MARYCLAIRE DALE

Posted: 09/12/2014 3:15 pm EDT | Updated: 09/12/2014 4:59 pm EDT



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Both the league and lead players' lawyers expect about 6,000 of the 19,400 retired players, or 28 percent, to develop Alzheimer's disease or at least moderate dementia. Dozens more will be diagnosed with Lou Gehrig's or Parkinson's disease during their lives, according to the data.

The reports were prepared for Senior U.S. District Judge Anita B. Brody, who is presiding over the class-action lawsuit in Philadelphia that accuses the NFL of hiding information that linked concussions to brain injuries. JA3435

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Data: 28 percent of NFL players will suffer Alzheimer's or dementia

AP

SEP 12, 2014 1:58P ET

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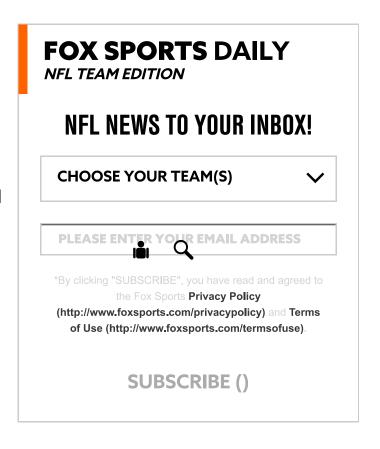
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nfl (http://www.foxsports.com/tag/nfl)











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NFL: 3 in 10 ex-players face Alzheimer's, dementia

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Associated Press

Published: 12 September 2014 01:05 PM Updated: 12 September 2014 09:55 PM

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NFL: 3 in 10 ex-players face Alzheimer's, dementia

Article by: MARYCLAIRE DALE Associated Press

September 12, 2014 - 3:55 PM

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file, Star Tribune

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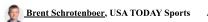
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NFL takes aim at \$25 billion, but at what price?



1:42 p.m. EST February 5, 2014

For the NFL to reach its revenue goal by 2027, fans, broadcasters and sponsors will have to pay more and more



(Photo: Kirby Lee, USA TODAY Sports)

NEW YORK (Jan. 31) — Sunday's Super Bowl at MetLife Stadium in East Rutherford, N.J., might be the most popular and expensive television program in U.S. history – about 110 million viewers watching a football game that commands nearly \$4 million for a 30-second commercial.

Tickets at the 50-yard line cost about \$10,000. A 20-ounce cup of Bud Light will cost \$14.

"Nothing is really sacred anymore," said John Vrooman, a sports economics professor at Vanderbilt University.

TICKETS: Market picking up steam late (http://ftw.usatoday.com/2014/01/super-bowl-ticket-prices/)

MANNING: Throws 'ducks' and proud of it (http://www.usatoday.com/story/sports/nfl/broncos/2014/01/30/peyton-manning-super-bowl-48-denver-richard-sherman/5051231/)

It won't stop there. The National Football League hopes to achieve \$25 billion in annual revenue by 2027, up from about \$10 billion now. Several analysts told USA TODAY Sports that the NFL can get there, but it will be an expensive journey. More palatial stadiums. Expanded playoffs. More exposure in more places, including smartphones, games in London and more Thursday night games sold to the highest-bidding network.

NFL Commissioner Roger Goodell gave the magic number at a meeting of NFL team owners in 2010: a goal of tripling league revenue in 17 years. If it happens, the NFL would have more income than the gross domestic products of dozens of small countries and would be in the same financial district currently occupied by gigantic global brands such as McDonald's, Nike and Goodyear Tire, each of which recently took in about \$21 to \$28 billion annually.

Who will pay the price? Fans, sponsors and broadcasters. The NFL remains the most popular sports league in America, and it commands a premium. If the average NFL fan thinks the cost of attending games is already too high, how about paying ever-higher prices to watch games on ESPN and the NFL Network? Cable and satellite TV providers pay ESPN an average of \$6.04 per subscription per month, more than double from 10 years ago and dwarfing the likes of CNN (63 cents) and TBS (72 cents), according to SNL Kagan, a market research firm.

COLUMN: John Elway's risky double down looking Super (http://www.usatoday.com/story/sports/nfl/super/2014/01/30/super-bowl-denver-broncos-elway-trading-tebow/5064267/)

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FIRING BACK: Colin Kaepernick pans Richard Sherman (http://ftw.usatoday.com/2014/01/richard-sherman-colin-kaepernick/)

"The standard (cable television) package that households receive is skyrocketing in cost at a point in the U.S. economy when we have increasingly lopsided distribution of income," sports economist Andrew Zimbalist told USA TODAY Sports. "Those two things have to collide."

The future

The NFL declined to release financial data, but an estimate of its revenue can be pieced together through various sources by economists and market researchers. That \$10 billion pie is roughly sliced four ways, according to Navigate Research, a Chicago-based firm that specializes in the evaluation of sports and entertainment marketing investments.

- About \$5 billion from media and television rights to broadcast games.
- About \$1-2 billion in sponsorships, such as its long-running deal with PepsiCo, worth about \$90 million to \$100 million per year.
- About \$2 billion related to attendance and ticket sales.
- · About \$1 billion in merchandise and licensing.

Growing to \$25 billion annually will require compound annual growth of about 7 percent, around \$1 billion per year.

CBS, Fox, NBC and ESPN provide the NFL with a total of about \$5 billion to \$6 billion annually from contracts that run through 2021-22. By 2027, Navigate Research predicts such media rights revenues could reach \$1 \(\text{A} \) billion annually from contracts that run through 2021-22. By 2027, Navigate Research predicts such media rights revenues could reach \$1 \(\text{A} \) billion annually from contracts that run through 2021-22. By 2027, Navigate Research predicts such media rights revenues could reach \$1 \) Abilion annually from contracts that run through 2021-22. By 2027, Navigate Research predicts such media rights revenues could reach \$1 \) Abilion annually from contracts that run through 2021-22. By 2027, Navigate Research predicts such media rights revenues could reach \$1 \) Abilion annually from contracts that run through 2021-22. By 2027, Navigate Research predicts such media rights revenues could reach \$1 \) Abilion annually from contracts that run through 2021-22. By 2027, Navigate Research predicts such media rights revenues could reach \$1 \) Abilion annually from contracts that run through 2021-22. By 2021, and a such a su

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That ambitious projection assumes that live NFL games will continue to be a golden goose for networks and their advertisers for one major reason: NFL games are one of the few remaining programs that huge audiences want to watch live instead of recording to watch later - fast-forwarding through the commercials that companies pay millions to air.

"We are firm believers that there is nothing more valuable in the world of TV than the NFL – nothing," said Michael Nathanson, a media analyst at MoffettNathanson, a stock research firm that specializes in the media and telecommunications industries. "Their ability to get to \$25 billion is kind of predicated on the staying power of the product. I think they're going to ask for whatever they need to from their broadcast partners, their cable partners."

UNFAIR? Seahawks player questions marijuana suspension (http://www.usatoday.com/story/sports/nfl/super/2014/01/29/seattle-seahawks-super-bowlbrandon-browner-limbo/5036123/)

STILL WAITING: Will Manning's backup ever start for Denver? (http://www.usatoday.com/story/sports/nfl/broncos/2014/01/30/brock-osweiler-backupsuper-bowl-peyton-manning-denver-russell-wilson/5068165/)

Vrooman, the Vanderbilt economist, says the NFL can get there primarily because it's a monopoly - the richest sports league on the planet with a business plan built largely through the Sports Broadcasting Act of 1961, which allows sports leagues to pool their television rights for sale to the highest bidder, protecting them from antitrust laws.

"The monopoly rule is to gouge half as many fans more than twice as much on everything," he said. He also predicts the league will become "increasingly more exclusive with the same general formula of fewer fans having access at higher prices to generate more certain media, venue and gate revenues."

The NFL disputes that, noting its commitment to broadcast some games on free over-the-air TV networks, which helps it reach bigger audiences. Even games on ESPN, for example, are available on free TV in local markets. But the league is not shy about its appetite for growth.

"We measure our business very simply: Is consumption going up, and is the economic pie growing?" said Brian Rolapp, the chief operating officer of NFL media.

Rolapp was involved in recent NFL deals with Verizon, Twitter, Microsoft and the television networks. He currently is involved in shopping a Thursday Night Football TV package and working on a new deal with DirecTV. He called the \$25 billion goal an aspiration.

"In order to get to a number that lofty, it requires a lot of different things," Rolapp told USA TODAY Sports. "It requires, clearly, hard work. It requires different thinking. We are relatively strong in our business. We're strong as a league, but what we always say around here is complacency is our enemy."

PHOTOS: ONE MEMORABLE SHOT FROM EVERY SUPER BOWL

The formula

For better or worse, the road to \$25 billion probably requires some variation of the following, analysts told USA TODAY Sports.

ONE GREAT PHOTO FROM EVERY

FULLSCREEN

More new and upgraded stadiums. This year's Super Bowl is in chilly New Jersey, a reward for the Jets and Glants building the swanky MetLife Stadium, which opened in 2010. Yet it has been 11 years since the Super Bowl was in 70-degree San Diego, where the Chargers still play in outdated Qualcomm Stadium.

To keep revenue growing, the NFL needs stadiums that are big moneymakers, such as AT&T Stadium, home of the Dallas Cowboys, where suites cost up to \$500,000 per year and fans pay more than \$80 for seats in the upper deck end zone. Levi's Stadium, the new \$1.3 billion home of the San Francisco 49ers, opens later this year and will host the Super Bowl in 2016. Later that year, the Minnesota Vikings will open their new stadium.

The risk for the NFL is that it might price out everyday, jersey-wearing fans, who might decide they'd rather watch games on high-definition TV anyway. Attendance accounts for only about about 25 percent of NFL revenue, and at times there have been signs of sagging demand. Three of the NFL's four first-round playoff games this year struggled to sell out. Will fans keep going to games if the price keeps rising and the view is better on TV?

"That is a big concern," Rolapp said. "It will always be an important part of the revenue ... We still believe it's still the best place to experience NFL football. I think it will be for some time, but we have to keep innovating so it remains that."

More weeknight games, anyone? The NFL has been shopping a Thursday night package to TV networks and could announce a buyer soon with possible simulcasting on the NFL Network, the league's cable outlet. NFL games once were mass-delivered for television consumption on Sunday afternoons and Monday night.

NBC, for example, pays about \$1 billion per year for its package of Sunday night games and playoff games.

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More televised content. If there's demand, create more supply. That's why the league is considering expanding the playoffs, creating another product to sell to networks eager to capture big live audiences. The NFL also is turning the offseason into a moneymaker by televising the NFL Combine in February and the NFL Draft in the spring, which has expanded from one day to three days, including two nights in prime time.

New markets. The NFL has been priming London as a market, with two sold-out games there last year and three games on tap in 2013. Meanwhile, Los Angeles hasn't had an NFL team since 1994. Moving existing teams from weak markets into bigger vacant markets might give team owners a better way to increase their shared revenue as opposed to adding more franchises to the 32-team league.

Conversely, Los Angeles has value to the NFL as a bargaining chip – the unstated threat of moving into that big, empty market can help existing franchises wring out taxpayer dollars for stadium upgrades and new construction.

Get ready for NFL teams to make "renewed threats of franchise relocation to leverage public money for private stadiums in the second venue revolution, just like the first (round of stadium upgrades) over the last two decades," Vrooman said. "Monopoly power over TV rights and franchise location is what provides the real engine for the economic growth of the most powerful sports league in the world."

VIDEO - SUPER BOWL QBs: PROFESSOR VS. APPRENTICE



Tom Pelissero, Rod Mackey, and Paul Silvi shine a magnifying glass at the QB match-up for the big game. Its old school vs new school Sunday at MetLife Stadium.

Phones, Internet and new media. More consumers get their news and information from their smartphones —a trend the NFL recognized with its recent \$250 million annual deal with Verizon to stream games onto phone screens. The NFL also recently made deals with Twitter and Microsoft's Xbox, giving it new revenue streams in growing interactive and social media.

With more viewers consuming video content online instead of on cable, cable companies and cable channels could see subscription revenue plummet. Those channels – including ESPN and the NFL Network – can try to recoup that revenue through online content, but it might not be as lucrative.

"The established content suppliers – NFL, ESPN – are uneasy and so going very slowly," said Roger Noll, emeritus economics professor at Stanford.

"They see the potential for a huge payoff, but also for a huge bursting of the bubble, and want to keep control until they know where things are likely to go."

Television. The NFL's TV rights contracts soon will be worth about \$7 billion per year combined, with most of them starting this year and lasting through 2022. What happens in 2023?

"It's a new day after that," Rolapp said. "We'll just have to see. A lot of things we do digitally along the way are a great experiment for us to see what the world will look like. We will be prepared one way or the other to be able to shift to where the consumer is."

To get to \$25 billion, the NFL probably needs about \$15-17 billion from networks.

If networks pay it, those costs likely will be passed down to the consumer. ESPN likely would ask for higher rates from advertisers and higher subscriber fees from cable distributors, and even viewers who don't like football would pay more because cable channels are not offered a la carte.

Case 18-2012 md Doc 18-60 B 00011831658201-Pa Fee 482)/06 Date Filed: 108/09/2019
"Everything else 10 years from now will be worth less relative to what the NFL is going to be worth," said Nathanson, the stock analyst. "No other sport has that kind of national draw to it,"

As long as the NFL can bring big live audiences, it'll be hard for the likes of ESPN to avoid paying up, but the growing risk is viewers who could decide to cancel their cable subscriptions and use other devices to watch what they want.

The NFL said it is committed to staying on free television, not just cable, where it has its own network and can reap cable subscription revenue in addition to advertising revenue.

"It would have been very easy years ago to migrate our games to cable," Rolapp said. "In fact, we could have gotten more money in the short term, it could be argued, if we would have done that. But we really are committed to a reach model and free television."

VIDEO: JERSEY HISTORY ON THE SEAHAWKS' SIDE



The daily report for Jan. 30, 2014, from Jill Savage at the Super Bowl.

Staying power

Much of this, of course, assumes that the NFL can continue to bring those live audiences well into the next decade.

Another risk to the league's long-term popularity is the concussion crisis. Amid lawsuits from former players, the league has vowed to make the game safer. This could mean changes in equipment and more rules that restrict bone-jarring hits.

"To the extent the NFL tries to pass new rules to reduce the force of hitting or the kind of hits you can make, I think it hurts the game," Zimbalist said. "And there signs that parents no longer want their children playing this game. I don't mean to predict doom for the NFL. I don't think there is doom, but the notion that they're going to get to \$25 billion seems to be excessively optimistic. I would not bet on that figure."

Rolapp, the Harvard-educated NFL executive, says the league maintains a "healthy paranoia" about all perceived risks, including pushing too much product onto fans. In the meantime, the NFL plans to stick to a simple formula.

"We're really in the business of aggregating America around events and around our game," Rolapp said. "There are fewer and fewer places that can do that. If you can aggregate audiences, you are going to be more and more valuable."

Follow Brent Schrotenboer on Twitter @Schrotenboer (http://twitter.com/schrotenboer). E-mail: bschrotenb@usatoday.com

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Report: NFL paid Roger Goodell \$35.1 million last year

By Ryan Wilson | CBSSports.com

February 14, 2014 3:25 pm ET



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Roger Goodell had a good 2013. (USATSI)

Two years ago, when NFL commissioner Roger Goodell was thought to make only \$20 million, Falcons wide receiver Roddy White sent this tweet:



Got some bad news for you, Roddy. Goodell more than doubled his pay over the next 12 months.

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NFL VIDEO

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(2:34)



To be clear: That's \$35.1 million -- plus another \$9.1 million in deferred payments -- for the year that ended March 31, 2013.

So how do we come across this information every year? Turns out, the multibillion-dollar money-making machine that is the NFL is, in the eyes of the government, a nonprofit organization. Thanks to an exemption written into the tax code, the league is exempt from federal corporate taxes.

(If you're so inclined, US Senator Tom Coburn (R-Okla.) explained the particulars in Wastebook 2012.)

The downside -- if you want to call it that -- to being classifed as a nonprofit: this Tax exemption also makes Goodell's salary publicly available, circumstances no doubt eased by the fact that he made nearly \$3 million a month.

in a letter obtained by Daniel Kaplan of the Sports Business Journal, NFL owners Arthur Blank, Robert Kraft and Jerry Richardson wrote to their fellow owners that "Goodell's compensation reflects our pay-for-performance philosophy and is appropriate given the fact that the NFL under his consistently strong leadership continues to grow."

Kaplan notes that the three owners comprise the league's compensation committee, adding that Goodell's salary almost certainly makes him the highest-paid sports executive.

Topics: Roddy White, Ryan Wilson, NFL



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NFL

NFL: The League That Runs TV

Owners Reach \$27.9 Billion Deal With Fox, CBS and NBC

By MATTHEW FUTTERMAN, SAM SCHECHNER and SUZANNE VRANICA December 15, 2011



NBC scored in the ratings Sunday as the Giants played the Cowboys. Getty Images

National Football League owners voted to approve \$27.9 billion of TV deals with Fox, CBS and NBC on Wednesday, confirming pro football as the driving force in an industry facing fundamental change.

As expected, the networks will pay 63% more on average to air NFL games from 2014 to 2022. Fox will pay an average of about \$1.1 billion for the National Football Conference package, which includes many of the league's biggest markets, say people familiar with the talks. CBS will pay about \$1 billion a year over the life of the deal for the American Football Conference package, which will include a handful of NFC games. And NBC will pay \$950 million a year for nine years for the Sunday night prime-time package.

The networks' willingness to fork over such enormous sums reflects the reality of television today. Audiences are fragmenting among hundreds of channels and alternative viewing options, such as the Internet. Football remains one of the few programs that still draws tens of millions of viewers who watch

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Vernon Davis of the San Francisco 49ers. *Getty Images*

live. That gives the networks much-needed leverage with both advertisers and cable operators, especially since the networks gained the right to stream the games on computers and tablets.

Overall annual broadcast revenue for the NFL will jump from an annual average of \$1.9 billion in the 2007-2013 period to nearly \$3.1 billion for 2014-22. Including deals with ESPN and satellite broadcaster DirecTV, the NFL will collect about \$6 billion a year in total TV revenue beginning in 2014, a figure that will likely increase the following year after the DirecTV deal expires. NBC is a unit of Comcast

Corp.'s majority-owned NBC Universal, while Fox is a unit of News Corp., which also owns The Wall Street Journal. CBS is a unit of CBS Corp., and ESPN is a unit of Walt Disney Co.

For many of the networks, the NFL is a break-even investment at best—but one they feel they have to make. NFL rights will account for roughly a quarter of the total programming spending by the four networks, including ESPN, by 2015, up from just over 20% in 2008, according to projections from SNL Kagan.

While TV advertising has generally grown slowly in recent years, advertising on NFL games has soared. Ad rates for NFL games rose 27% to \$347,800 for a 30-second spot last season, compared with the 2007 season, according to WPP's Kantar Media. The cost of a similar nonsports prime-time ad, by contrast, fell 14% last year from 2007. And the total amount advertisers spent on NFL advertising

last season, about \$3.3 billion, is up over 20% since the

The NFL reached a \$27.9 billion deal with Fox, CBS and NBC for the rights to broadcast games from 2014 to 2022, Matthew Futterman reports on Markets Hub. Photo: REUTERS.

More NFL News

League Owners Signs Off on Jaguars Sale
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2007-2008 football season, according to Kantar. Overall TV advertising on U.S. broadcast and cable networks grew just 3.5% between 2007 and 2010 to \$44.3 billion.

Experts don't see NFL ad demand slowing anytime soon. "It won't break until the consumer breaks with lack of interest and ratings fall," says Tony Ponturo, a sports marketing consultant and former media and sports marketing czar for Anheuser-Busch.

Mark Lazarus, the chairman of NBC Sports, says NFL football is simply too popular not to have. "We think it's one of, if not the, premier television property," he says. "It has value to us for reaching consumers, for diversifying our affiliates and giving our advertising sales team a mix."

So far this fall, NFL games have averaged 17.8 million viewers at any given minute, more than almost all regularly scheduled programs, according to Nielsen data. Importantly, many of those viewers are young men, who are hard for advertisers to reach through other programs. And the fact that most consumers watch NFL games live is important at a time when many viewers record shows and then skip the commercials when they watch them later.

The NFL "is almost a necessity for broadcast and cable networks in terms of maintaining the health of their business overall," says Kris Magel, director of national broadcast at Initiative, a media-buyingunit of

10/1/2014 Caseate-20122mdDoctMeht Toosetest Gestovin Page 43996 Date Filed: 2018/09/2019 Interpublic Group of Cos.

At the same time, though, at least in some cases the NFL is eating up advertising dollars that would have ended up elsewhere on television. "For us it comes out of other TV budgets," says Steve Shannon, vice president of marketing for Hyundai Motor America. "Big important media properties are more valuable than ever."

Still another reason for networks to pay up for the NFL: The popularity of NFL games gives them a big weapon in disputes over subscription fees with cable, satellite and telecommunications companies that sell TV service. Big broadcast networks like Fox and CBS have increasingly sought those fees to supplement ad revenue, and CBS, for instance, has said it expects to bring in more than \$250 million a year in subscription fees by the end of 2012.

"The subscription component is really important going forward, because that's how they're going to get more money out of cable companies," says Deana Myers, a senior analyst at SNL Kagan.

But sports fees are helping to drive up cable rates, raising concerns among media executives that consumers will soon balk at the increasing cost of television.

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SBJ/20100405/This Week's News

Goodell sets revenue goal of \$25B by 2027 for NFL

By Daniel Kaplan, Staff Writer

Published April 5, 2010

NFL Commissioner Roger Goodell wants the league to reach \$25 billion in revenue by 2027, an amount that would mean adding nearly \$1 billion in new revenue on average each year until then.

Goodell presented the futuristic figure late last month to owners at their annual league meeting in Orlando. While the number is designed to serve more as an ambitious goal than a true financial projection, it underscores the degree to which the NFL, under the nearly four-year tenure of Goodell, has sought to dramatically expand its business, whether in technology or overseas.

"It has happened in a lot of well-run businesses," New York Jets owner Woody Johnson said of the kind of revenue growth suggested by Goodell. "If we expend our capital, expand our stadiums, keep renovating and keep all of our capital equipment up to the highest standards, invest in technology, [invest] in the business, it could be done — or more."

Tripling revenue in a roughly 17-year time frame is something the NFL has already accomplished, though off a much smaller base. Precise comparable revenue figures could not be obtained, but growth can be seen in part by looking at the salary cap, which is based on a percentage of revenue. The cap in 1994 was \$34.6 million. After several blockbuster national TV contracts and a surge in NFL popularity, league revenue last year hit \$8.5 billion, lifting the cap to \$128 million, a more than threefold increase from 1994.

"It is certainly an aggressive number," Dallas Cowboys Chief Operating Officer Stephen Jones said of the \$25 billion figure, "but it is certainly one we would like to get to."

Tripling revenue over the next 17 years, however, could prove tougher than doing so from the mid-1990s until now. Fox Sports broke the bank in 1994 to become an NFL broadcaster in order to establish the channel's credibility, and DirecTV was added with its first out-of-home package. Only a few teams are currently in need of new stadiums whereas in the early to mid-1990s, the NFL's stadium boom had just begun. In addition, the U.S. sponsorship and advertising markets are more fully developed and committed to sports financially than they were in the 1990s, when sports as a business wasn't the size of industry it is today.

There would have to be similar events — and on larger scales — in the future for a comparable growth rate. Areas that hold potential include Internet, cell phone, satellite and international, as well as the NFL Network.

"If you take the number of fans in the [United] States, 181 million, there is clearly massive upside internationally," said Mark Waller, the NFL's chief marketing officer, who is pushing for more foreign games. "We should be measuring our fan growth globally as we do in the U.S., and a key driver will be more games."

Another area is technology. The league just signed a four-year, \$720 million sponsorship/media deal with Verizon that will see both games and the league's RedZone channel streamed to cell phones. Neither streaming to mobile nor RedZone were options just a few years ago, Johnson noted, saying that the revenue Goodell foresees could come from categories that do not exist today.

In addition, reaching a new labor deal is critical to the desired increase in revenue. The NFL and NFL Players Association are battling over the looming expiration of the collective-bargaining agreement next March, and a prolonged labor stoppage could



Roger Goodell's goal would mean an average revenue increase of \$1 billion a year.

damage the league. Also, the owners say the game will not grow without an economic deal that allows them to invest with a reasonable rate of return.

The union has responded that it is willing to provide the owners financial credits where the league can prove the money is being used to grow the sport, but to do this the NFL must provide audited financial reports, something Goodell and the owners have said no to so far.

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This Week's News

NFL

Former players: Devil is in the details with NFL concussion settlement

Print



BY DON BANKS

Posted: Thu Aug. 29, 2013 Updated: Mon Jun. 16, 2014



"The guys who need it now won, but the rest of us have lost the ability to take the bully behind the shed," Former NFLPA president Kevin Mawae said.

Don't try telling former NFL players union president **Kevin Mawae** that Thursday's concussion litigation settlement was an even-handed resolution to the most contentious and significant issue facing the sport as the NFL's 2013 regular season looms.

Mawae, a retired 16-year NFL veteran and two-term NFLPA president, said only the ex-players in the most dire need of financial and medical assistance truly won a victory with Thursday's announcement of a \$765 million mediated settlement.

"I think the league won big on this, because the players settled for a pittance," Mawae told SI.com, on the phone from his home near Baton Rouge, La. "It's a relative drop in the bucket. I'm not going to say the players caved, because it would do an injustice to the older men who really need the help now, but at some point in time, the collective body of players, retired and active, have got to be willing to go all the way to the wall with this issue.

"They didn't this time. The league won this hands down. I know as soon as you print that there's going to be a bunch of former players pissed off at me for saying that, but it's true. The league won."

KING: The NFL's nuclear-winter scenario has vanished

Mawae, the former Seahawks', Jets' and Titans' center, did not add his name to

the list of roughly 4,500 ex-NFL players who sued the league over the effects of brain injuries they contend were incurred on the field, saying he knew football posed inherent risks all along, but they were worth the rewards.

But the settlement is a setback for players in the long run, Mawae said, because it keeps the NFL from having to release information in court about what it knew in regards to the connection between brain injuries and football, and when it knew it. And that opportunity lost represents a discovery process that can't have a dollar value placed upon it.

"Everybody had been asking me what was going to happen with the lawsuit, and I've said all along they're going to settle it," said Mawae, who retired after the 2009 season.

"Because in the end, settling it for however much money is a whole lot better for the league than giving up everything they have as far as information and potentially harming the shield for good. There's too much potential for information that could have done damage to the NFL, and it's better to just pay it off with \$765 million, plus court costs."

Peter King: The owners win in concussion settlement

The MMQB's Peter King call the NFL owners the winners in the concussion lawsuit.

The NFL's class of elderly retired players understandably cannot be blamed for not being able to afford to take the long view in regards to the concussion litigation settlement. The different agendas between that group of ex-players, and those of Mawae's era, made Thursday's development capable of being seen from vastly different perspectives.

"If it helps the neediest men, in the most dire situations, then, yes, it's a good day," Mawae said. "But it depends on how long it takes for them to get that money. If those guys who are destitute, or have no insurance, or have struggles with dementia, if they can get this help immediately, that's a positive. Especially the older players who helped lay the foundation of this game. We owe them that."

But today's players, and those recently retired, lost out, Mawae said.

"The guys who need it now won, but the rest of us have lost the ability to take the bully behind the shed," he said. "From my standpoint, I'd rather take the bully behind the shed and beat the crap out of him, and let him know he can't bully us

around. But now, essentially what we've done is taken a little bit of our milk money back and gotten the promise that he won't touch us again.

"But there's no ability to go and finish off the fight. The league, at the end of the day, was willing to spend \$765 million, plus another \$200 million in legal fees, and that's like spending the Jacksonville Jaguars in order to not have to divulge information you had that the players could have used to finish the fight. It's like taking it 99 yards, but not getting that last yard."

McCANN: Here's what happens next in the concussion lawsuit settlement

Several ex-NFL players SI.com spoke to acknowledged that the devil is in the details in a deal as complicated as the concussion litigation settlement, and said they are still waiting to see if the agreement can be executed swiftly and fairly. One of those was ex-Bucs defensive lineman Chidi Ahanotu, 42, a 12-year NFL veteran who signed his name to the concussion litigation and recruited ex-Tampa Bay teammates Hardy Nickerson, Eric Curry and Mike McGruder to do the same.

"It's decent money, but the key part of this will be the people who determine who qualifies and who's eligible," said Ahanotu, who played for five teams between 1993-2004, spending nine seasons in Tampa Bay. "If it's like the NFL's disability benefit program, this isn't a win for the players. That panel denies most requests. We have access to the benefits, but that doesn't mean you get them.

"That's why the jury is still out on this. I want to say we won, but you can't do that until you see how this money can be accessed and by whom. The fact that this money is here is great, but [how the money is distributed] is the most important JA3465

part of the process. That's everything."

Ahanotu said he has suffered from memory loss and a lack of mental clarity since his playing career ended, and worries that his long NFL career will lead to future cognitive issues. He was not surprised by Thursday's settlement, but thought the negotiation process would take longer.

"I was expecting them to settle, because it's just a PR nightmare for the NFL," he said. "Now that the season is close to starting, the league doesn't want this issue looming over everything. But I thought it'd take longer than this."

Reached as he was about to go on Fox Sports1 to talk about the concussion litigation settlement, former Saints linebacker Scott Fujita, now an NFL analyst on that network, was trying to quickly digest the news and impact of the agreement.

"It looks good on paper, and the press release sounds fantastic, all that kind of stuff," said Fujita, who did not join the lawsuit. "But we're all trying to figure out the details and what they mean. That will tell the story."

Cowboys quarterbacks coach Wade Wilson, himself a former NFL quarterback of 17 seasons, called the settlement a potential "win-win for both sides," in that it hopefully allows for closure for the league and its players on this issue.

"Any time you can get care to the ex-players who are really needing it, that's a phenomenal thing," said Wilson, who did not join the lawsuit and said he didn't even know any former teammates who had. "I really do think it's a good day for the NFL, because any time there's litigation out there and you get it resolved, it's a plus. Hopefully now we can start to put it behind us and move on to football and the games."

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NFL

Deal in Concussion Suit Gives NFL a Big Victory

By MATTHEW FUTTERMAN and KEVIN CLARK

Updated Aug. 29, 2013 11:22 p.m. ET

After years of damaging publicity, the National Football League reached a surprise settlement with a group of 4,500 former players who sued it over concussion-related issues.

The settlement represents a major victory for the NFL. Just a week before the 2013 season, the league has largely removed an issue that has dogged it for years and led some to suggest the sport should be banned.

The agreement, reached at 2 a.m. Thursday Eastern time after nine weeks of intense mediation, came far earlier than most expected. It calls for the NFL to pay \$765 million, mostly for medical benefits and injury compensation for the retired players, in addition to funding medical research and covering legal expenses.

The settlement includes all retired NFL players who present medical evidence of severe cognitive impairment, not just those who joined the suit.

The NFL admitted no wrongdoing or liability in the agreement, which must be approved by Anita Brody, the federal judge in Philadelphia overseeing the case. She is likely to approve the agreement, said a person familiar with the matter.

The plaintiffs don't have to approve the settlement, but anyone can opt out, a league spokesman said.

Layn Phillips, a former U.S. District judge who mediated the settlement, said in a statement that it would "provide relief and support where it is needed at a time when it is most needed," while avoiding a long legal process.

"This settlement is a very important step for ensuring that future generations of football players do not suffer the same way that many in my generation have," said Kevin Turner, an NFL running back in the 1990s and a lead

The National Football League and 4,500 former players suing the league over concussion-related issues reached an agreement on a settlement. WSJ's Kevin Clark and NFL Hall of Fame quarterback and SmallBizClub.com Founder and CEO Fran Tarkenton discuss. Photo: AP.



Former Chicago Bears quarterback Jim McMahon in 1987. (AP Photo/Doug Jennings) Associated Press

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plaintiff who suffers from amyotrophic lateral sclerosis, a motor neuron disease known as Lou Gehrig's disease.

The settlement will cost each of the NFL's 32 franchises \$24 million over 20 years, or roughly \$1.2 million a year. Projected league revenues this season are \$10 billion, and the NFL finalized a series of media-rights deals last year

that guarantee more than \$40 billion through 2022.

The agreement doesn't prevent future players from making claims or suing the NFL for injuries incurred while playing. But because all current players are party to the current collective-bargaining agreement between the NFL's owners and the league's players' union, those claims would be handled through the arbitration process outlined in the labor deal.

NFL Executive Vice President Jeffrey Pash, who spearheaded the case for the league, called the deal "an important step that builds on the significant changes we've made in recent years to make the game safer, and we will continue our work to better the long-term health and well-being of NFL players."

The lead plaintiffs' attorney, Christopher Seeger, said the settlement is an opportunity for the most severely affected players to get medical coverage quickly and covers retired NFL players for the next 60 years. Former players who suffer from ALS, Parkinson's disease, Alzheimer's disease, dementia and other neurological conditions will receive "substantial benefits," some as high as \$5 million, he said.

Mr. Seeger said the deal will "get help quickly to the men who suffered neurological injuries. It will do so faster and at far less cost, both financially and emotionally, than could have ever been accomplished by continuing to litigate."

Legal experts familiar with the case say the plaintiffs' attorneys didn't believe they had enough firepower to win in court. NFL lawyers were prepared to probe each plaintiff about his athletic history to try to convince the court the NFL couldn't be held liable for injuries that could have come from youth, high-school or college football—or substance abuse.

John Goldman, a litigator with Herrick, Feinstein LLP, who was following the case, said the plaintiffs had "tough legal hurdles," given the inability of players to prove what caused their injuries.

Current executives at the NFL Players Association issued a terse statement: "All of the plaintiffs involved are part of our player community, and we look forward to learning more about the settlement."

Kevin Mawae, a former president of the NFLPA who wasn't a plaintiff, said the settlement was far too small. "Basically, for the cost of their least valuable team, the NFL was able to remove a huge monkey off their back," Mr. Mawae said. "But even worse than the money, it's that they don't have to admit guilt and the players will never be able to know the information that the league knew about this issue."

Big Settlements

NFL (2013): The professional football league and a class of former players agreed to settle a concussions-related lawsuit for \$765 million. The NFL generated \$9.5 billion in revenue in 2012.

Goldman Sachs (2010): The bank paid \$550 million to settle its civil litigation with the Securities and

He said, "At end of the day it's a very small price to pay considering the negative outcome that could have happened to the NFL if the players had taken this to court."

The settlement calls for \$75 million of the NFL payment to go to baseline medical exams for ex-players, \$675 million to go toward compensation and \$10 million to go to

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Exchange Commission, which charged that Goldman profited off the housing market's collapse by selling clients mortgage securities. The firm reported \$34.1 billion in revenue last year.

Countrywide (2011): Bank of America settled for \$335 million a discriminatory mortgage-lending suit filed by the Justice Department against its Countrywide unit. BofA reported \$84.2 billion in revenue last year.

Dow Corning (1998): The company agreed to settle a lawsuit related to its silicone-breast implants for \$3.2 billion. Its revenues in 2012 were \$6.1 billion.

Tobacco (1998): The four largest cigarette makers in the U.S. settled state claims for \$206 billion to be paid over 25 years.

research and education.

The cost of notifying members of the class won't exceed \$4 million. Legal fee payment will be determined by the district court. The NFL will pay 50% of the settlement over the next three years, then the balance over the next 17 years.

If the initial funds are exhausted, the NFL will have to contribute a maximum of \$37.5 million to supplement the fund, bringing the total to just over \$800 million, not including legal fees, which are expected to be as much as \$100 million, according to a person familiar with the matter.

Players in the suits include Pro Football Hall of Famers Chris Doleman and Bruce Smith and recent stars such as former Jacksonville Jaguars running back Fred Taylor.

Families of players with chronic traumatic encephalopathy who have been posthumously diagnosed, including those who committed suicide as did former NFL linebacker Junior Seau, also will be eligible for millions of dollars in compensation, Mr. Seeger said.

Former Minnesota Vikings quarterback Fran Tarkenton said the deal is a good one for the players, simply because most older players have little money. "They are just broke, they've got dementia, they've got ALS, all types of brain damage and what this does, it puts the money into these people to let them live their live with some type of dignity."

Helmet maker Riddell, a party in many of the lawsuits, wasn't a part of the settlement, Mr. Seeger said. A Riddell spokesman declined to comment.

—Ben Cohen contributed to this article.

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Thursday, August 29, 2013

Reaction to the concussion deal

ESPN.com news services

Reaction to Thursday's order from Senior U.S. District Judge Anita Brody outlining a proposed \$765 million settlement between the NFL and more than 4,500 former players who want to resolve concussion-related lawsuits:

"From the outset of this litigation, I have expressed my belief that the interests of all parties would be best served by a negotiated resolution of this case. The settlement holds the prospect of avoiding lengthy, expensive and uncertain litigation, and of enhancing the game of football." -- Brody

"It's a great day. My preference was when players were done playing, we'd have some kind of aftercare. It's a great thing for both sides of football that guys can get aftercare now. That's the most important thing." -- former NFL quarterback <u>Mark Rypien</u> to USA Today Sports

"It's frustrating. Frustrating. And to have a 10-year-old daughter who says to her mother, 'Daddy can't do this because Daddy won't remember how to do it,' it's not a good feeling. I'm glad to see there's been ... acknowledgment that football has had something to do with a lot of the issues us players are going through right now." -- former <u>Dallas Cowboys</u> running back Tony Dorsett

"Concussions are part of the game. I know a lot of the old players need a lot of help, and it's quite a settlement, from what I understand. ... I think people have hid behind this too long. It's time it's out in the open. It's out in the open now so we'll see what happens." -- former Chicago Bears coach and ESPN analyst Mike Ditka

"I'm not a part of it, but it seems fair. There have been a lot of guys that have suffered. Take Sam Huff, I saw him carried off the field on a stretcher twice in one game. I'm glad they're addressing it. I hope the players are satisfied and they're taken care of." -- former NFL quarterback Sonny Jurgensen

"They (the NFL) put a big settlement number out there, but guess what? They say you have to qualify, how easy will they make that? Then you get 50 percent in the first three years and the rest of it you have to wait for over a period of 17 years? Some of the guys who need to be compensated will be dead by then. A guy who has alzheimer's now. ... how relevant is that number to them? Who cares?" -- former NFL running back Leroy Hoard

"From what the first offer was to where it is now, I think it's a fair deal. The thing that I'm happy about is they are going to take of some of these guys that are really affected by this. They will do the baseline testing and get these guys the help that they need, more so than the money." -- Hall of Fame quarterback

"I'm surprised, I'm surprised it ended. I'm surprised they settled. There's a lot of older guys, guys older than me that are ailing right now, suffering so I can understand that you can say 'OK, I'll take the short term gain.' But it doesn't fix the problem. The thing that gets me is I still wanna know what is the NFL not telling us? I have been trying to figure it out. I have gone through this, gone through my first training camp and I remember getting my helmets and pads the first time and I've never had anyone tell me about concussions or anything like that so I want to know what the NFL is not telling us. But I'm happy for the guys that are part of the settlement." -- former Rams defensive tackle D'Marco Farr.

"I hope this settlement is the NFL saying, 'We're taking concussions seriously. We're going to keep working on it.' The worst case scenario for me is the NFL saying, 'We paid you money. Now go away.' ... "It felt like for the longest time we were making stuff up, that we were after money. I would give \$200 million for my dad to be back here and be alive. There's no price on the hell you go through with this." -- Garrett Webster, son of former Steelers center Mike Webster, who died in 2002 from brain disease.

"At the surface it looks like a good deal. But in the long run i don't think it is. That's usually how it works when it comes to players and ownership. ... I'm pretty sure (the lawsuit) changed things. There's a certain protocols and fine systems and safety precautions that are being taken back on the field because of them trying to get ahead of lawsuits and stuff like that that come up later. I think that's affected how the game's being officiated and rule changes and stuff." -- Texans left guard Wade Smith





"I am able to live my life the same way I was, but now -- chances are, I am 44 now, I won't make it to 50 or 60 -- I have money now to put back for my children to go to college and for a little something to be there financially. ... The compensation provided in this settlement will lift a huge burden off the men who are suffering right now, for both them and their families, of course. It will give them the peace of mind to have the best quality of life they can have. No longer have to make decisions regarding their health based on what they can afford, but based on what is the best treatment for them." -- former NFL running back Kevin Turner, who has Lou Gehrig's disease.



The settlement includes much-needed medical care and monitoring of former players, as well as a commitment to research funding. -- The Boston University Center for the Study of Traumatic Encephalopathy, which has been examining brains of deceased NFL players to try to determine what sort of connection exists between football and brain disease.

The NFL is far and away the most popular spectator sport in this country, so it has a symbolic power to lead the way on this issue. Now they are free to help raise awareness and fund prevention and treatment that will save millions from an injury that affects what it means to be human. -- agent Leigh Steinberg in op-ed on Forbes.com.



"I'm shocked that it is settled. I'm used to the NFL taking a hard-line approach as they have throughout the years with strikes and everything else. I'm curious how they came up with the figure and I've got a lot

10/1/2014 Cases 182012nd-D0606nent: 0053111931658091-1110age 14505049 100ate Pitege 08/09/22019 of questions, but I am happy that it's done. Any time the NFL acknowledges they are ready to settle

something, it shows they knew they had some sort of negligence." -- former offensive lineman Lomas Brown, a seven-time Pro Bowler who had sued the league



Information from ESPN's Kelly Naqi, ESPN.com's Nicholas Wagoner, Scott Wagner and The Associated Press was used in this report.

EXHIBIT 48





SportsDay

Dorsey Levens rips settlement of concussion lawsuit against NFL

Sept. 18, 2013

One of the segments that aired Tuesday night on HBO's "Real Sports with Bryant Gumbel" dealt with the issue of the \$765 million settlement of the NFL concussion lawsuit.

Former Green Bay Packers running back **Dorsey Levens** was interviewed at length about his reaction to the settlement.

The correspondent on the story, **Jon Frankel**, also interviewed **Christopher Seeger**, the lead attorney for the plaintiffs, and **Kevin Turner**, a former NFL player who suffers from ALS, known as Lou Gehrig's disease.

Both Levens and Turner were among the more than 4,500 plaintiffs in the lawsuit. Levens said he was upset about the decision to settle. He wanted the case to go to trial.

"This is a great victory for them," Levens said. "I didn't understand how they got off so lightly."

Levens, who played for Green Bay from 1994-2001, was asked what his expectations were for the lawsuit.

"It was about getting guys help," Levens said. "You know, and when a guy calls me and says, 'I've called the NFL five times. I can't get a response. My head hurts all the time. And if I can't get help, I'm going to take care of it.' I couldn't sleep. What do you say to a guy like that? I'm going to do my best to help you out."

Levens wanted a trial that could have cost the NFL billions and forced the league to reveal that it knew all along players were at risk.

"I wanted to know what they knew and when they knew it," Levens said.

Seeger defended the amount of the settlement.

"I think we got every nickel we could get," Seeger said. "I know the NFL has lots of nickels. But we got every nickel that we could get."

Seeger said the players' case was not without its weaknesses

"I'm not making the argument for the NFL, but as the lawyer for the players, I have to recognize one thing about this case," Seeger said. "Many of the players, you know, who play two or three years in the 10/1/2014 NFL, four years in the NFL, spent more time playing football outside the NFL."

Frankel asked Turner if he thought "the NFL got away cheap."

Said Turner: "If you call three quarters of a billion cheap, certainly. And to them, maybe it is. Maybe they're behind closed doors, laughing their (expletive) off. But so far the people that I've seen that are complaining, I don't think any of those people are symptomatic right now. The people that have dementia, ALS are happy with it. You know, because they need it now."

Levens said he was happy for those like Turner who are able to get help from the suit but said he worried about future cases.

Levens was asked if he thought he had any traumatic brain injury symptoms.

"I do," Levens said. "The sleeplessness, the blurred vision, the ringing in the ears. You know, some irritability. It's there."

Levens said his nightmare is that he could suffer the same fate as Turner and that there was nothing he could do to safeguard himself from what might happen.

"It's too late," Levens said. "If there was any damage, it's already done. Now you just got to wait and see. Now you play the waiting game, which is terrifying in itself because the first time you forget where your keys are, you know, you kind of lose — it's just like — it's happening. You know, any little thing that happens, you start to question it."

Levens said the lawsuit's conclusion is not really an ending.

"This issue's not going away," Levens said. "Just because the lawsuit is over, this concussion issue is not going away. It's just the tip of the iceberg."

Fixing the blame

ESPN.com asked its readers: "Which is more to blame for the bizarre ending to the Wisconsin-Arizona State game?"

Out of the nearly 19,900 responses, 70% answered "the officials" and 30% said the "Wisconsin offense."

In the state-by-state breakdown, no state's majority of voters thought the Wisconsin offense was more to blame.

In Wisconsin it was 85% officials and 15% Wisconsin offense.

In Arizona, it was 53% officials and 47% Wisconsin offense.

Pitcher's pitch goes awry

New York Mets pitcher Matt Harvey, interviewed Wednesday on "The DanPatrick Show," took product endorsement to a particularly irritating level.

Instead of talking about his elbow injury, he kept plugging Qualcomm. Harvey later apologized for his annoying patter on the show.

10/1/2014

Harvey has decided to rehab instead of undergoing surgery on his arm.

During the discussion with Patrick about that issue, Harvey said: "I strongly believe that that's going to work and pay off but today, I'm here talking about Qualcomm and hoping I can help them out as much as possible."

Harvey then went on and on about Qualcomm, until Patrick mercifully ended the segment.

Said Patrick: "Man, that's a bummer. That's the first time we had him on....That was bad. That was bad. And I wasted people's time there."

Call SportsDay at (414) 223-5531 or send email to <u>bwolfley@journalsentinel.com</u>

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Check the box to include the list of links referenced in the article.

EXHIBIT 49

Seau family says 'no' to NFL settlement

Lawyer says deal doesn't cover heirs or ensure public airing of concussion issues

By Greg Moran (/staff/greg-moran/) 10:06 a.m. Sept. 3, 2014 Updated 6:19 p.m.



Linebacker Junior Seau at a press conference Friday March 14, 2003 at Seau's the restaurant in Mission Valley. — John Gastaldo

The family of San Diego Chargers great Junior Seau won't be part of a proposed settlement between the National Football League and thousands of former players who sued over health problems attributed to repeated concussions.

The decision to withdraw from the settlement means the Seau family will pursue its own wrongful death lawsuit against the league, said Steven Strauss, attorney for the family.

It also may imperil the proposed settlement, to which a federal judge gave preliminary approval in June. Seau is perhaps the most prominent name involved in the litigation, as his suicide in 2012 rocked the league and its fans and heightened attention on the growing concussion crisis.

Strauss said the proposed deal does not address the wrongful death claims the family has sued under and will not provide compensation for relatives of former players, such as Seau's four children. Under the terms of the pending deal, the family would get \$4 million.

"The settlement provides medical benefits and compensation for certain players, for past damages," Strauss said. "It doesn't include compensation to heirs or successors."

Strauss said the family also wants more information about the concussion and head trauma issue to come out.

"They want to know what happened to their dad," he said. "This settlement isn't designed for that. Not one deposition has been taken. Not one document has been produced."

The decision by the family could start a domino effect, as other players and families may decide to follow suit. That could break up the entire deal.

Anyone opting out of the deal has until Oct. 14 to notify the federal judge overseeing the case in Pennsylvania. A hearing that would finalize the settlement is set for Nov. 19.

Christopher Seeger, a New York attorney who was the chief negotiator for the settlement on behalf of the players, said in a statement that other players should not follow Seau and risk giving up the "tremendous guaranteed benefits" they would get.

"If Mr. Strauss believes the \$4 million his client is eligible for under the settlement is insufficient, he can choose to permanently forfeit these benefits and face all the significant risks associated with continued litigation," he said.

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Also on Wednesdescent for in the suit under a complex formula weren't enough, among other criticisms. By objecting, the former players remain in the suit but tell the judge what they don't like. It's different from opting out, which removes a party from the case.

More than 4,500 players are involved in the suit, alleging a variety of wrongdoing by the league that includes claims of fraud for how it handled concussions and other brain injuries. An original settlement deal in 2013 provided for \$675 million in compensation for all players who claimed some kind of brain injury as well as funds for testing and research. Lawyers for the players would also get \$112 million.

The deal was roundly criticized, and U.S. District Judge Anita Brody questioned if the compensation fund was large enough. In July, after the league agreed to remove the cap on damage claims, a revised settlement agreement was given preliminary approval by the judge.

While there is no longer a cap, the settlement contains a grid that details how much a player would get based on age and diagnosed ailment. For example, someone under 45 diagnosed with Lou Gehrig's disease would get \$5 million.

Seau played 20 years in a Hall of Fame career, but while in the game and after retiring in 2010, he suffered from insomnia, depression, anxiety, alcohol abuse, mood swings and emotional detachment. He shot himself once in the chest on May 2, 2012, at his Oceanside home.

After his death an evaluation of his brain by the National Institutes of Health concluded he had evidence of chronic traumatic encephalopathy, or CTE, a degenerative brain disease, likely the result of repetitive head trauma as a linebacker.

Shaun Martin, a law professor at the University of San Diego School of Law, said it's rare to see enough people opting out of a settlement in a class-action lawsuit so as to scuttle the settlement. Seau's move was not surprising.

"You would rather not have someone as high profile as Junior Seau opt out," he said. "But anyone who really thought about it knew he would. He has uniquely powerful claims, about the NFL causing his suicide. Even more bluntly, it's not in the ballpark of what the estate of Junior Seau would take to settle the case."

The family lawsuit was filed in San Diego Superior Court in January 2013, alleging among other things the league concealed the dangers of concussions and head trauma from players for years.

The league has consistently denied such allegations.

It's unclear what will now happen to the suit, said Strauss, a partner at the law firm Cooley LLP. He said he wanted the Seau case sent back to San Diego to proceed. But it is also possible that Brody, the Pennsylvania judge, could hold on to this case, and any other "opt -out" cases, until the larger settlement is finalized.

That could take several years, if any party to the settlement decides to appeal to the federal courts.

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EXHIBIT 50

Hall of Famer Joe DeLamielleure will object to NFL concussion deal



Pro Football Hall of Famer Joe DeLamielleure doesn't believe the NFL has the best interest of its former players at heart. (Mark Duncan / Associated Press)

By NATHAN FENNO

SEPTEMBER 4, 2014, 3:50 PM



oe DeLamielleure, the Pro Football Hall of Fame offensive lineman, plans to object to the proposed NFL concussion settlement.

"I'm going to tell everyone I know to object," said DeLamielleure, who played for the Buffalo Bills and Cleveland Browns from 1973 to 1985, in a recent interview with The Times.

The information packet mailed to each retired player that includes a 24-page summary of the proposed settlement didn't assuage DeLamielleure's concerns. Neither did an August meeting, in Canton, Ohio, before the Pro Football Hall of Fame inductions, with attorneys who negotiated the settlement.

A longtime critic of the NFL and NFL Players Assn., DeLamielleure doesn't believe many of the

estimated 20,000 retired players will receive monetary awards from the proposed settlement. He is also frustrated by a variety of other issues in the settlement that were granted preliminary approval by a federal judge in July, including retired players' having to pay \$1,000 to appeal an awards decision. The money would be refunded if they win.

Retired players have until Oct. 14 to object or opt out of the settlement. If enough retired players object, DeLamielleure believes they can unravel the settlement.

"It's going to take 4,000 to 5,000 guys to object or opt out," he said. "But I bet there's not even 4,000 or 5,000 guys who know this is going on."

On Wednesday, an attorney for the family of the late San Diego Chargers linebacker Junior Seau announced they would bypass a potential \$4-million award and opt out of the settlement to continue wrongful-death litigation against the NFL on their own.

Others are waiting to make a decision on their participation until they know the outcome of next week's hearing in the U.S. Court of Appeals for the Third Circuit in Philadelphia, where seven retired players asked the court to intervene in the proposed settlement.

"Any objection threatens to delay approval of this settlement and endanger its guaranteed benefits for retired players who are in desperate need," plaintiffs' co-counsel Christopher Seeger said in a statement. "We look forward to finalizing this agreement so that former NFL players can soon begin taking advantage of its benefits."

A fairness hearing is scheduled for Nov. 19 in Philadelphia in front of U.S. District Judge Anita Brody.

Follow me on Twitter: @nathan fenno.

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EXHIBIT 51

ensued about 17 hours after the ingestion of the poison, important quantities of the poison were found in the stomach. Brandl and Tappeiner ¹⁰ and Gadaskina and Shtessel ¹¹ presented data on the excretion of fluoride through the gastrointestinal tract, and Charnot ¹² described fluoride excretion in the bile. Thus it is possible that gastroenterohematic circulation of fluorine compounds exists. Because of these data and the high toxicity of fluoroacetate repeated gastric lavages seem to be advisable.

1522

The total quantity of fluoroacetate recovered from the organs and body fluids tested was 465 mg. Since the patient weighed approximately 140 lb. (63.5 kg.), disregarding the fluoroacetate present in organs from which no sample was available for toxicological study, he ingested a minimum of 6 mg. per kilogram of fluoroacetate.

The therapy used in this case was essentially symptomatic: barbiturates to decrease convulsions, intracardial procaine hydrochloride to inhibit ventricular fibrillation, atropine sulfate to decrease bronchial mucus secretion, and plasma transfusion and oxygen to offset vasomotor and respiratory failure. Experimental studies have suggested the use of certain specific antidotes.⁶ Of these

monacetin was directed for the treatment of this case; however, it arrived too late to be employed.

SUMMARY

- 1. A case history of fluoroacetate poisoning has been described together with postmortem examination and chemical analysis of the fluoroacetate content of organs and body fluids.
- 2. It appears that there is no important difference between postmortem findings of sodium fluoroacetate and sodium fluoride poisoning. The additional biochemical effects of sodium fluoroacetate thus seem to have no pathological manifestation of diagnostic significance.
- 3. Because of indications of gastrointestinal excretion and reabsorption of fluorine compounds, repeated gastric lavages seem to be advisable.
 - 4. Other therapeutic aspects are briefly discussed.
 - 1921 Walnut St. (Dr. Harrisson).
- 10. Brandl, J., and Tappeiner, H.: Über die Ablagerung der Fluorverbindungen im Organismus nach Fütterung mit Fluornatrium, Ztschr. f. Biol. München u. Leipz. 10:518, 1891-1892.
- 11. Gadaskina, I. P., and Shtessel, T. A.: Resorption, Distribution and Elimination of Fluorine After Experimental Poisoning with Sodium Fluoride, J. Physiol. U.S.S.R. 19: 1245, 1935.
- 12. Charnot, A.: Influence de quelque composés minéraux sur les effets toxiques du fluorure de calcium, Bull. Acad. de méd., Paris 120: 224 (Oct. 18) 1938.

ELECTROENCEPHALOGRAPHIC CHANGES IN PROFESSIONAL BOXERS

Ewald W. Busse, M.D.

and
Albert J. Silverman, M.D., Denver

Since the days of the Roman gladiators, men have fought each other and other persons have watched. The sport of boxing, as it exists today, is largely the product of psychological forces that have not changed in essence for 2,000 years. It is the feeling of many persons that in spite of periodic criticism and the efforts to ban prize fighting, the sport will persist. Since it appears unlikely that athletic contests requiring physical contact will ever cease, the physician should attempt to safeguard the physical and mental health of the participants.

Much has been accomplished to protect the athlete in such sports as football and ice hockey, but protective measures for the amateur and professional pugilist have not kept pace. Jokl ¹ in his monograph (1941), which is concerned with the medical aspects of boxing, recognized and deplored this situation, and he collected a wide va-

riety of case material that was representative of possible sequelae due to boxing injuries. Raevuori-Nallinmaa ² in a recent publication states his belief that the usual cause of death related to boxing is intracranial hemorrhage. Tragic and sobering though they be, deaths of this kind are relatively rare. More important, and certainly much commoner, are the mild psychic changes observed in a high percentage of boxers. These changes are due to brain damage, which is also responsible for the less frequently seen, so-called "punch-drunk" person, who is in fact in a state of traumatic dementia and reveals severe psychic and neurological abnormalities.

The syndrome of boxing encephalopathy is probably due to multiple concussion hemorrhages as well as to contusion and laceration of the brain. The "knockouts" and "technical or near knockouts" (representing states of commotio cerebri) are usually the result of a trauma that alters brain function. If the trauma is severe or is mild but repeated at intervals that do not permit the brain to return to normal functioning, permanent damage may result

Many investigators have reported on the value of the electroencephalogram in the detection of brain injuries. Dow, Ulett, and Raff,³ in doing electroencephalograms of persons immediately after injury, reported that a

Professor of Psychiatry (Dr. Busse), and Resident in Psychiatry and Electroencephalography (Dr. Silverman).

Mr. W. Asmus, Executive Director, and Mr. E. Bohn, Chairman of the State Athletic Commission of Colorado, assisted in the preparation of this study.

From the Electroencephalograph Laboratory of the Colorado Psychopathic Hospital and the Division of Psychosomatic Medicine, University of Colorado Medical Center.

^{1.} Jokl, E.: The Medical Aspect of Boxing, Pretoria, S. Africa, J. L. Van Schaik, Ltd., 1941.

^{2.} Raevuori-Nallinmaa, S.: Brain Injuries Attributable to Boxing, Acta psychiat. et neurol., supp. 60, p. 51, 1951.

mild cerebral trauma produced electroencephalographic changes that decreased in abnormality within a few minutes. If amnesia was associated with the trauma, but the patient was clear-minded when his record was taken, there was only a slight increase in the percentage of abnormal records. If consciousness was at all impaired at the time of the electroencephalogram, there were invariable, accompanying electroencephalographic changes. Abnormal findings recorded immediately after head trauma may become normal, however, for Dow and associates found that a larger number of records were abnormal when taken less than a half hour after injury. This points to some mechanism in concussion other than such factors as petechia, contusion, and emboli, each of which would take several days to disappear. Williams 4 found invariable electroencephalographic changes accompanying altered consciousness as a result of head injury and stated that concussion is the result of widespread disorganization of cerebral function. Strauss 5 found diffuse slowing in patients with clouded consciousness but noted a more selective slowing in frontal areas of patients showing facetiousness. Ward and Clark 6 indicated that concussion or localized blows to the cortex resulted in changes in the electroencephalogram identical to those produced by rapid rises in intracranial pressure. Jokl ¹ supported this by his contention that at the moment of the blow to the head there was a sharp rise of intracranial pressure.

In their experimental studies Zimmerman and Putnam 7 reported that minimum cell changes could occur without electroencephalographic changes but found that when the trauma was severe enough to cause "incompletely reversible cell changes" there was a direct relationship between severity of cell changes and severity of electroencephalographic abnormalities. They also reported a reduction in voltages that was directly proportional to the amount of force applied. Heppanstall and Hill 8 stated that focal findings were generally significant of symptomatic rather than idiopathic disorders and that there was a greater chance of permanent electroencephalographic changes in persons who sustained head injuries when they were under the age of 20. Kaufman and Walker 9 reported that in about two-thirds of their patients convlusive disorders developed after acute and severe head injuries. Abnormal electroencephalograms were seen in 90% of those patients in whom seizures developed and in more than 75% of those without seizures. Focal abnormalities were noted in over 80% of the epileptics and in over 65% of the nonepileptics. Greenblatt,10 reporting on post-traumatic patients with convulsions, fainting spells, psychoses, or other personality disorders, found that 68% had disturbed electroencephalograms. Regarding minor head injuries, Harris and co-workers 11 stated that abnormal waves may be found in hyperventilation only and that a good prognosis can be made from serial electroencephalograms in which the tracings become more normal. Other investigators, in discussing electroencephalographic changes following head injury, reported different findings. Amplitude asymmetries 12 and bursts of six to eight per second activity 13 were noted by some, while others 14 reported decreases in voltage and increases or decreases in frequency.

Thus, it is evident that the electroencephalogram has no specific pattern in head injury and that any abnormality may be seen, depending on whether there is a temporary physiological disturbance or actual organic damage. The site of injury also has some bearing on electroencephalographic findings.

METHOD AND PROCEDURE

In order to help prevent serious injuries or death, the state athletic commission of Colorado, acting on the recommendation of one of the authors of this article (E. W. B.), unanimously passed a regulation requiring periodic electroencephalographic examinations on all professional boxers performing in Colorado. Although several states recommend the examination in specific cases, the authors do not know of any other state in which such electroencephalograms are compulsory. The regulations as set up by the state athletic commission were as follows: 1. A professional boxer must have an electroencephalogram at least once a year. 2. In the case of a "knockout," an electroencephalogram must be done within two weeks of the injury. 3. Frequent, repeated examinations could be done in the case of a boxer with suspicious recording.

Our purpose in this article is to record the results obtained from the first year's electroencephalograms as an initial report and to attempt to evaluate the worth of the electroencephalogram in safeguarding the health of those who participate in boxing. A Grass eight-channel electroencephalograph was used. So-called active lead placements were left and right frontals, motors, occipitals, and anterior and posterior temporals. Reference electrodes included the ears and vertex leads. Additional leads were used in specific cases as indicated. Records were classified according to the method described by Gibbs, Gibbs, and Lennox. 15 Activation with hyperventilation was performed routinely. Monopolar and bipolar tracings were done in each case, and a natural sleep record was obtained whenever possible.

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RESULTS

Thirty electroencephalograms as outlined above were done on 24 boxers. Their age distribution (divided arbitrarily into four groups) was as follows:

No. of Men	Age Group, Yr.
3	18-20
12	21-23
ā	24-26
4	27-29

Of the electroencephalograms done on these men, 4 showed severe disturbance, 5 were moderately dysrhythmic, and 15 were within normal limits; thus, the total number of records showing disturbance amounted to 37.5% of the series. This is well above the 10 to 15% reported by Gibbs, Gibbs, and Lennox 15 and others in control groups, whose findings are in accord with those in our own control series. 16 These figures have statistical significance in that there are only three chances in a hundred that they are due to coincidence.

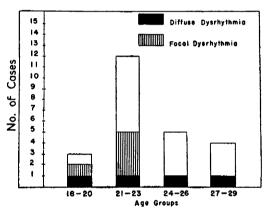


Fig. 1.—Incidence of abnormal electroencephalograms in boxers by age groups.

Type of Abnormality Seen.—There were four records showing severe disturbance. Three of these showed a temporal slow-wave focus, and one revealed diffuse slowing and paroxysms. Five records showing moderate disturbance were noted. Three of these were diffusely slow, and two were indicative of temporal slow-wave foci. Thus, in totaling the severely and moderately disturbed records, five were found to be focal and four showed diffuse findings. (In addition, paroxysms were seen in one each of the focal and diffuse records.) One record showing diffuse disturbance was found in each of the four age groups, while all the focal disturbances were present in the two youngest age groups. It was also noted that, although abnormalities were found in each age group, records showing disturbance seemed to be more frequent in the youngest men; but because of the few cases involved, this could not be statistically corroborated (fig. 1). In order to evaluate the report of decreased voltages in post-traumatic cases, 14 our records were also reviewed with this in mind, and six were found in which voltages were generally decreased. This was not significantly more than the 20% of low-voltage records expected in normal persons.

When we attempted to correlate history of knockouts with electroencephalogram disturbance, the following facts were noted: Ten of the 24 fighters had been knocked out in their ring careers at least once. Four of the 10 had dysrhythmic records, three being severely

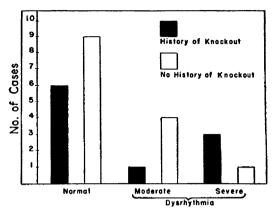


Fig. 2.—Comparative electroencephalographic findings of boxers with and without a history of knockout,

abnormal and one only moderately so. In the remaining 14 fighters, none of whom had ever been knocked out, one record showing severe disturbance and four showing moderate abnormalities were found. Because the number of records under study was not large enough, these findings are not statistically significant. It is noteworthy, however, that although there was an equal number of records showing disturbance in both groups, the men who had been rendered unconscious had electroencephalograms showing the severer disturbances. These findings were consistent with those of other investigators previously mentioned (fig. 2).

An attempt was also made to determine if length of ring career could be correlated with electroencephalographic disturbances, but no correlation was found. Elec-

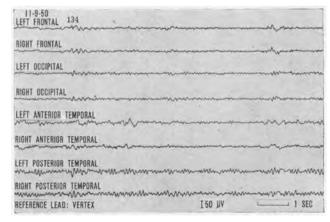


Fig. 3.—Initial electroencephalogram of professional boxer in case reported. Note the slow-wave focus in the left anterior temporal area.

troencephalograms showing severe disturbances were seen in boxers who had been in from 2 to 50 fights, moderate dysrhythmias in men who had had from 1 to 15 fights, and normal records in men who had participated in from 1 to 106 fights. This lack of correlation is commented on below.

^{16.} In our control series of 329 patients, whose ages ranged from 18 to 54 years, it was noted that 36 (10.94%) showed moderate disturbances and 10 (3.04%) severe dysrhythmias, so that the total of records showing disturbance was 13.98%.

REPORT OF A CASE

The patient, a professional boxer, aged 21, was first seen by us in November, 1950. He had had three professional fights prior to his first electroencephalogram. In July, 1950, he was knocked out, but the following month he won his next fight by a technical knockout in the first round. Three days before a scheduled fight in November, 1950, the patient had his first electroencephalogram, which revealed a left temporal slow-wave focus.

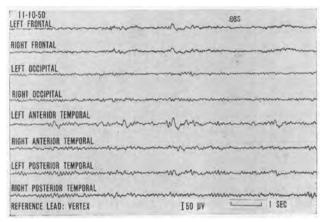


Fig. 4.—Repeat electroencephalographic examination of boxer in case reported. By comparison with figure 3, the focal disturbance now appears to consist of higher amplitude and slower waves.

The fight was cancelled. A repeat electroencephalogram revealed more extensive temporal focal findings. (The patient, incidentally, showed no abnormal neurological or psychological signs or symptoms at any time.) He was temporarily suspended from boxing, but continued to train. A third electroencephalogram in January, 1951, revealed the persistence of the focus and the addition of paroxysms. This suggested that he had received additional brain injury during the period of training, from which he could not legally be prohibited. It was now believed that this man had suffered some degree of irreversible damage, and he was permanently suspended from boxing on Jan. 16, 1951, for his own good. It was felt that in this case the electroencephalogram had picked up intracranial damage before it had become clinically apparent and that late neurological disability or even death had possibly been averted by this decision (fig. 3, 4, and 5).

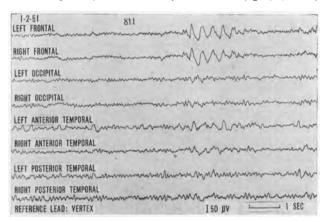


Fig. 5.—Final electroencephalographic examination of boxer in case reported. Note the persistence of the left anterior temporal slow-wave focus and its occasional reflection in the right temporal area. Note also the brief paroxysm of slow waves occurring in the frontal area.

COMMENT

Even in this small group of professional boxers used as a pilot study, it was at once apparent that their series of electroencephalograms were more frequently abnormal than those seen in control studies. It was noted that as many disturbed records were seen in the group who had not been knocked out as in their more unfortunate colleagues. In spite of this there was some indication that those who had definitely been knocked out showed severer disturbances. It should be pointed out that very little background material was actually available to us; for example, the number of times a man had been hit severely enough to cause him to be dazed without actual loss of consciousness, the number of amateur fights, and the extent and severity of training were not known. Thus, because of lack of such information, the correlation between number of professional fights and the electroencephalogram reading had no apparent meaning.

Concerning the abnormalities seen, diffuse records were found in every age group, while focal records were confined to the younger men. Thus, abnormal findings appeared more frequently in the younger age groups because of this very preponderance of focal records in them. These findings support the well-known fact that focal disturbances are good evidence of actual brain damage. There were relatively fewer records showing disturbance in the older men in our study. One can speculate that these men, for the most part, had been fighting for years and, having escaped brain damage in their first fights, were more experienced and better able to avoid injury in the ring. In addition, attention should be directed to the established fact that there are individual differences regarding susceptibility to trauma, so that in any group of boxers exposed to injury over a period of time it is likely that the more susceptible men are soon damaged permanently and retire from the ring, leaving their less susceptible fellows to carry on. An interesting clinical observation made during this study was that the men who showed focal temporal electroencephalographic abnormalities appeared to be, generally speaking, much more aggressive while fighting; and it is our feeling that this aggressiveness, together with the hint of impaired judgment as noted, may be associated in some way with the temporal lobe foci seen in these men. We feel that case material provided by boxers will provide much information about minor repeated head injuries, and future, better controlled, more extensive studies on larger groups may bring much interesting knowledge to light.

SUMMARY AND CONCLUSION

Compulsory electroencephalographic examinations were made on 24 professional boxers with the cooperation of the state athletic commission of Colorado. A statistically significant, increased incidence of dysrhythmic electroencephalograms was found in nine boxers (37.5%) in our series. There was some indication that men who had been knocked out showed severer electroencephalographic disturbances than those who had not been knocked out. Focal disturbances were more frequent in the younger men than in the older men, who also, generally speaking, had fewer electroencephalographic disturbances. A case of a boxer is presented who was finally suspended from boxing largely on the basis of progressive encephalographic abnormalities. From the above findings it is concluded that periodic, compulsory electroencephalographic examinations contribute to the protection of boxers and should be a required part of routine examinations.

4200 E. Ninth Ave. (Dr. Busse).

EXHIBIT 52

PUNCH DRUNK *

HARRISON S. MARTLAND, M.D. NEWARK, N. J.

For some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as "punch drunk." Fighters in whom the early symptoms are well recognized are said by the fans to be "cuckoo," "goofy," "cutting paper dolls," or "slug nutty."

Punch drunk most often affects fighters of the slugging type, who are usually poor boxers and who take considerable head punishment, seeking only to land a knockout blow. It is also common in second rate fighters used for training purposes, who may be knocked down several times a day. Frequently it takes a fighter from one to two hours to recover from a severe blow to the head or jaw. In some cases consciousness may be lost for a considerable period of time.

The early symptoms of punch drunk usually appear in the extremities. There may be only an occasional and very slight flopping of one foot or leg in walking, noticeable only at intervals; or a slight unsteadiness in gait or uncertainty in equilibrium. These may not seriously interfere with fighting. In fact, many who have only these early symptoms fight extremely well, and the slight staggering may be noticed only as they walk to their corners.

In some cases periods of slight mental confusion may occur as well as distinct slowing of muscular action. The early symptoms of punch drunk are well known to fight fans, and the gallery gods often shout "Cuckoo" at a fighter. I know of one fight that was stopped by the referee because he thought one of the fighters intoxicated.

Many cases remain mild in nature and do not progress beyond this point. In others a very distinct dragging of the leg may develop and with this there is a general slowing down in muscular movements, a peculiar mental attitude characterized by hesitancy in speech, tremors of the hands and nodding movements of the head, necessitating withdrawal from the ring.

Later on, in severe cases, there may develop a peculiar tilting of the head, a marked dragging of one or both legs, a staggering, propulsive gait with the facial characteristics of the parkinsonian syndrome, or a backward swaying of the body, tremors, vertigo and deafness. Finally, marked mental deterioration may set in necessitating commitment to an asylum.

Of course the symptoms produced by the late manifestations of epidemic encephalitis, by the juvenile and presenile types of paralysis agitans, by syphilis, brain tumors and other forms of cerebral injury may so closely resemble those of the condition punch drunk as to be differentiated only with extreme difficulty or not at all. Nevertheless, the occurrence of the symptoms in almost 50 per cent of fighters who develop this condition in mild or severe form, if they keep at the game long enough, seems to be good evidence that some special brain injury due to their occupation exists.

As far as I know this condition has practically not been described in medical literature. I am of the

*Read before the New York Pathological Society, at the New York Academy of Medicine, New York, May 10, 1928.

*From the pathologic department of the City Hospital, and the office of the chief medical examiner of Essex County, N. J.

opinion that in punch drunk there is a very definite brain injury due to single or repeated blows on the head or jaw which cause multiple concussion hemorrhages in the deeper portions of the cerebrum. Such hemorrhages are very apt to occur in or near the corpora striata, in the corona radiata but almost never in the cerebral cortex or below the tentorium cerebelli. These hemorrhages are later replaced by a gliosis or a degenerative progressive lesion in the areas involved. Therefore, in late stages the symptoms often mimic those seen in diseases characterized by the parkinsonian syndrome. I realize that this theory, while alluring, is quite insusceptible of proof at the present time, but I am so convinced from my former studies on post-traumatic encephalitis that this is the logical deduction that I feel it my duty to report this condition.

MULTIPLE CONCUSSION HEMORRHAGES

As this theory of punch drunk assumes that the basic lesion is due to traumatic multiple hemorrhages, it will be necessary to discuss briefly this type of brain injury.

In 1924 Cassasa 1 reported five autopsies showing what he called multiple traumatic cerebral hemor-In all these cases there was a history of head Three patients were momentarily unconscious at the time of injury. After a lucid interval varying from three to twenty-four hours there developed a period of marked irritability with increase of deep reflexes, which was followed by unconsciousness. At autopsy, sections of the brain showed multiple usually punctate hemorrhages scattered over various parts of the parenchyma of the brain. Lacerations of the scalp, fractures of the skull, cortical lacerations or hemorrhages except for occasional slight pia-arachnoid hemorrhages were not found. Microscopic examination showed these punctate hemorrhages to be located around the blood vessels in the perivascular spaces of Virchow-Robin. When large, they broke through into the surrounding parenchyma and often became confluent. Cassaca considered this type of traumatic cerebral hemorrhage as relatively rare, for he had found only these five cases during a period of ten years' work with Dr. Otto Schultze, former coroner's physician, and Dr. Charles Norris, chief medical examiner of New York City.

Cassasa's explanation of the mechanism of concussion depends on the existence of the so-called perivascular and perineuronal spaces and the identification of a network of fine fibrils connecting the external wall of the blood vessel with the surrounding brain tissues across the spaces of Virchow-Robin.

Cassasa says:

Sudden overfilling of the perivascular lymph space with cerebrospinal fluid conceivably could produce laceration of a vessel by the tearing of its wall in the neighborhood of such a fibrillar attachment. Otherwise, without such an attachment, the laceration of a vessel surrounded by fluid could not be produced by any pressure exerted through that fluid which would only tend to compress the vessel but not lacerate it. Such an increase of cerebrospinal fluid in one perivascular space could be caused by the cerebrospinal fluid from the surface of the brain being driven into it by pressure exerted by the change of shape of the skull—the result of a blow or This change of shape under an area of violence is in the direction of flattening and diminution of space for the cerebrospinal fluid in that area. This fluid must find its way out of that area through the various sulci of the brain and in connection therewith such fluid as cannot find its way

I. Cassasa, C. B.: Multiple Traumatic Cerebral Hemorrhages, Proc. New York Path. Soc. 24: 101 (Jan.-May) 1924.

through these channels must find a way into the perivascular lymph spaces in the reverse direction of the normal flow of the cerebrospinal fluid in these channels.

The modus operandi of Cassasa's theory may be roughly illustrated in figure 1.

The existence of perivascular spaces is still questioned. Some observers think they are artefacts, and others assert that they exist only under pathologic conditions. The consensus, however, supports the original conception of His (1865) that there exists a system of richly intercommunicating spaces in the nerve tissues and around the blood vessels. The work of Weed in this connection is well known.

In 1927, Osnato and Giliberti ² studied 100 clinical cases of concussion of the brain with or without fracture of the skull and one of Cassasa's cases from a histologic standpoint. They concluded that:

Anatomic and clinical investigations seem to show definitely that our conception of concussion of the brain must be modified. It is no longer possible to say that "concussion is an essentially transient state which does not comprise any evidence of structural cerebral injury." Not only is there actual cerebral injury in cases of concussion but in a few instances

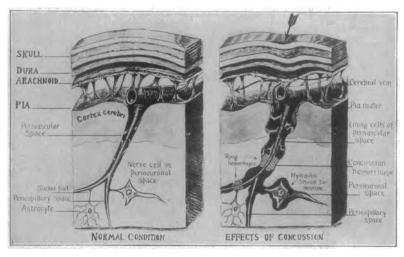


Fig. 1.—Schematic diagram of normal perivascular and perineuronal spaces on the left, and the probable mechanism of production of concussion and multiple concussion hemorrhages on the right.

complete resolution does not occur, and there is a strong likelihood that secondary degenerative changes develop. When this happens, we have a condition which, clinically at least, resembles some of the reactions seen in encephalitis. We feel, therefore, that the postconcussion neuroses should properly be called cases of traumatic encephalitis.

In 1927, Martland and Beling * reported their experience with consecutive cases of traumatic cerebral hemorrhage over a definite period of two years. During this period, 309 consecutive autopsies were analyzed of people dying as the result of cerebral injuries (exclusive of gunshot wounds of the head), occurring in a community of about 800,000 people and representing practically all the deaths due to cranial injury during that period. The number was sufficiently large to give a pretty good idea of the incidence of the various types of traumatic intracranial hemorrhages.

Extradural hemorrhage was found in twenty-five cases, or 8.2 per cent; cortical laceration and hemor-

rhage in 254 cases, or 82 per cent, while hemorrhages similar to those described by Cassasa and unassociated with fracture of the skull or other gross surface injuries occurred in nine cases, or 2.9 per cent. Unclassified subdural and pia-arachnoid hemorrhages and multiple, streaky, deep hemorrhages associated with cortical injuries were present in twenty-one cases, or 6.9 per cent.

Cortical laceration and hemorrhage characterized by laceration of the vessels of the leptomeninges with hemorrhage in the pia-arachnoid and cortex of the brain constituted by far the most frequent and important traumatic lesion within the cranial cavity. It was usually associated with a fracture of the vault, often running into the base of the skull.

The object of this paper was to call attention to the frequency of the type of hemorrhage described by Cassasa and to its great importance in relation to the various sequelae that often follow head injuries.

When the skull was fractured this type of hemorrhage did not occur, since the splitting of the skull at the time of the violence seemed to prevent the increased intracranial pressure with consequent displacement of

cerebrospinal fluid. The frequency with which these hemorrhages occurred in or near the corpora striata was first noted, as well as their rarity in the cerebral cortex or below the tentorium cerebelli.

The location of these hemorrhages naturally must depend on the laws of hydrostatics as applied to the cranial cavity, about which there is still much to learn. Their frequency in or near the basal ganglions is probably explained by a displacement of spinal fluid from the cisterna interpeduncularis, by the effects of contrecoup, into the perivascular spaces running along the vessels supplying these parts. When the corona radiata is involved the fluid is probably displaced from the subarachnoid spaces over the outer surface of the brain by the direct or contrecoup effects of the violence.

The infrequency of these hemorrhages in the brain stem and cerebellum is due to the protective influence of the tense and firm

tentorium cerebelli which takes the force and protects the underlying structures, and to the fact that in most cranial injuries the force is applied to the vault or sides of the skull.

While this type of traumatic hemorrhage was apparently recognized by those performing medicolegal autopsies, its significance from a clinical standpoint had not been appreciated.

The possibility of fat embolism causing some of these hemorrhages was first recognized by Cornwall,⁴ who had examined one of Cassasa's cases and found evidence of such emboli in the brain. Fat embolism presents the only serious argument against the mechanical theory of Cassasa. It can be demonstrated at autopsy after nearly all fractures of the long bones, and also has been seen after operations on obese subjects, especially such as radical amputation of the breast and herniotomy for umbilical hernia. Bissell ⁵ believes that it may explain certain deaths following these operations formerly attributed to surgical shock. The increased

^{2.} Osnato, Michael: and Giliberti, Vincent: Postconcussion Neurosis Traumatic Encephalitis, Arch. Neurol. & Psychiat. 18: 181-211 (Aug.)

<sup>1927.
3.</sup> Martland, H. S., and Beling, C. C.: Traumatic Cerebral Hemorrhage, read before the American Neurological Association in May, 1927, at Atlantic City, N. J.

^{4.} Cornwall, L. H.: Personal communication to the author.
5. Bissell, W. W.: Pulmonary Fat Embolism: A Frequent Cause of Postoperative Surgical Shock, Surg. Gynec. Obst. 25:8-22 (July) 1917.

viscosity of the venous blood causes a rise in the venous pressure and a fall in arterial pressure similar to that seen in shock.

It is generally agreed, however, that fat embolism rarely causes serious symptoms or results fatally. Most of the fat reaches the lungs and is held there. As Shinkai 6 has shown, this is due to the high viscosity of the fat, to the tortuosity and distensibility of the capillaries of the lungs, to the low blood pressure in the pulmonary artery, and to the fact that the pulmonary circulation constitutes the first filter for fat which enters the venous circulation. At autopsy, oil droplets may be seen with the naked eye in the blood from the right heart, large veins and lungs, provided proper autopsy technic is used.

In some cases a considerable amount may reach the systemic circulation and cause petechiae in the skin and pleura and microscopic evidence of fat in the brain, spleen and kidneys. Systemic emboli are more likely to occur if the foramen ovale is patent and in such cases multiple, punctate hemorrhages have been seen throughout the white matter in enormous numbers after a simple fracture of the femur. In six of the nine cases reported by Martland and Beling the injuries were limited entirely to the head, and fat emboli were eliminated.

The mechanical theory of Cassasa best explains most of these hemorrhages, although fat embolism might occasionally produce similar lesions. The ringlike distribution of these hemorrhages about the vessels is not characteristic of trauma alone. A similar location is seen in fat embolism, arsenical encephalitis and hemorrhagic forms of influenza encephalitis. In epidemic encephalitis the ringlike perivascular arrangement of the inflammatory cellular, defense reaction is similar in its anatomic location.

It is conceivable that the milder forms of concussion may be attributed to distention of the perineuronal spaces causing hydraulic shock to the neurons without the occurrence of actual hemorrhages.

I believe that such hemorrhages form the foundation of a replacement gliosis which explains the occurrence of post-traumatic symptoms in many cases of head injury in which recovery occurs. It forms the best possible explanation of the large and important groups of postconcussion neuroses and psychoses and the so-called post-traumatic encephalitis.

Even at the present time there is a strong tendency among some writers to demarcate concussion from contusion both clinically and anatomically. based usually on the assumption that concussion is unaccompanied by demonstrable morphologic alterations. Miller 7 has recently stated that concussion is the result of disturbed equilibrium of the cortical cells especially. After producing unconsciousness in animals by repeated blows on the head and administering trypan blue intravenously, his failure to produce any staining of the brain was attributed to the absence of brain injury. Mention is not made of microscopic Examinations of the brain in any of these animals, and the mechanism of the production of the unconscious state in animals by repeated blows on the head must be vastly different from that of a single blow applied to the human cranium.

FATAL CASE ILLUSTRATING MULTIPLE CONCUSSION HEMORRHAGES

The following case, taken from the series reported by Martland and Beling, is abstracted here as an illustration.

Case 1.—History.—A man, aged 76, while going upstairs, stumbled and struck his head. He became unconscious. He did not vomit. On admission to the hospital he was in coma. The pupils were small and unequal. There was a laceration over the left eyebrow with brush abrasions on the left side of the face. The upper and lower eyelids of the left eye showed ecchymosis, the ocular conjunctiva being free from hemorrhage. He died thirty hours after admission to the hospital with pulmonary edema, having never regained consciousness.

Autopsy.—There was a small amount of hemorrhage in the left temporal muscle and overlying scalp, and laceration of the outer part of the left eyebrow. The skull was not fractured. There was marked edema of the brain, with dilatation of the lateral ventricles. There was no laceration or hemor-

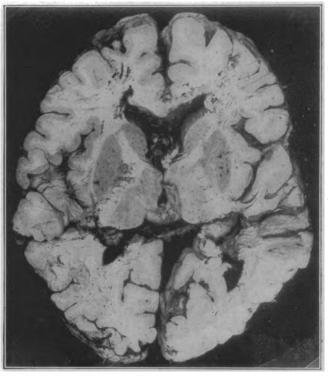


Fig. 2.—Brain in case 1: Multiple punctate concussion hemorrhages may be seen situated chiefly in the corona radiata of both frontal lobes and in the corpora striata. Other brain injury is absent.

rhage of the surface of the brain. In the corona radiata of both frontal lobes were multiple, punctate hemorrhages. There were innumerable small hemorrhages less than a pinhead in size in the white matter of the brain over the roofs of both lateral ventricles. There were a few similar areas in both corpora striata and over the ependyma of the third ventricle and in the posterior horns of the lateral ventricles.

PUNCH DRUNK AND ITS RELATION TO POST-TRAUMATIC ENCEPHALITIS

Unfortunately there is no previous record of any statistics compiled by competent medical authorities as to either the existence or the nonexistence or incidence of the condition known as punch drunk. There are no previous medical reports to my knowledge of its symptomatology, progress or end-results. We are placed in the position of accepting a series of objective symptoms described to us by laymen. There is undoubted proof that for years fighters, fight pro-

Shinkai, T.: Experimental Fat Embolism, Beitr. z. path. Anat.
 z. allg. Path. 78:109 (Aug.) 1927.
 Miller, G. G.: Cerebral Concussion, Arch. Surg. 14:891 (Jan.) 1927.

moters and the sporting world have recognized and talked about this condition. One sporting writer of note has recently stated that punch drunk was greatly exaggerated and that he had consulted eminent neurologists who had assured him that such a condition did not exist. I have found that the opinion of shrewd laymen, many of whom are making a living by observing the physical fitness, actions and characteristics of the professional fighter, is perhaps more substantial than the opinion of medical experts.

A fight promoter whose ability to judge the physical condition of fighters is unquestionable has given me the names of twenty-three fighters whom he considers punch drunk. Many of these men are scattered over the country and I have been unable to ascertain their exact condition at the present time, especially those who are in asylums. I have examined five of these men and they present the clinical pictures as described.

As an illustration I will report one case of advanced parkinsonian syndrome due to punch drunk:

Case 2.—History.—N. E., aged 38, born in the United States, started to fight in 1906 when 16 years of age. He stopped fighting in 1913, when 23 years of age, because of a tremor in his left hand and an unsteadiness on his legs. During his period of fighting he was a professional featherweight and soon became a top notcher. He had fought such men as Charlie Griffin, Jack Britton, K. O. Brown, Tommy O'Toole, Harry Stone, Kid Burns, Kid Tuts, Johnny Baker, Teddy Maloney and Tommy Lang. He had been knocked out twice;

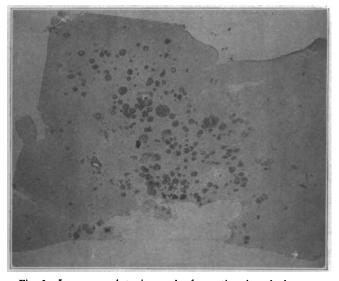


Fig. 3.—Low power photomicrograph of a section through the corpora striatum in case 1: Innumerable "ring hemorrhages" may be noted with their perivascular distribution.

once when 22 years of age he was out for an hour. He was never sick and seldom drank. On account of symptoms of tremor and unsteadiness, he was often wrongly accused of being intoxicated. Since 1913 his condition has slowly progressed until he now resembles a well marked case of paralysis agitans.

Examination.—The patient is a well nourished and apparently healthy man. His gait is staggering and propulsive, his facial expression masklike. There is marked stammering and hesitancy in speech. He has a fine tremor in his hands and tongue. The pupils are equal and react to light. The knee kicks are slightly exaggerated. Clonus and Babinski phenomenon are absent. The sensations are normal. The intelligence is normal. He has been under treatment in many clinics for paralysis agitans and told that his fighting did not have anything to do with his present condition. The blood Wassermann reactions have been repeatedly negative. Complete serologic examination of the spinal fluid was entirely negative.

From a neurologic aspect this case is one of paralysis agitans. It either is traumatic in origin or is a primary, essential form of paralysis agitans of the juvenile type. Epidemic encephalitis is eliminated in this case, since the first symptoms appeared in 1913, three years before epidemic encephalitis was first recorded in France at Bar le Duc, four years before it appeared in Vienna, and six years before cases were making their appearance in America.

CONCLUSIONS

1. Very definite anatomic-pathologic proof exists that following a cranial injury death may occur in which the autopsy discloses no other lesions but multiple punctate hemorrhages in the deeper structures of

List of Fighters Known by One Promoter to be "Punch Drunk"

			·	
No.	Initials	Class	Has Fought	Present Condition
1	B. N.	LHW	Joe Gans	Parkinsonian syndrome
2	J. D.	HW	Weinert, Fulton	Drags leg; bad shape
3	J. T.	$\mathbf{L}\mathbf{W}$	Leonard, Kansas,	Drags leg; talks slow
	n n		Dundee, Tendler	
4	В. В.	LW	Walker, Tendler	Punch drunk
5	w. J.	LW	Dundee, Leonard	Punch drunk
6	F. <u>J.</u>	$\mathbf{H}\mathbf{W}$	Willard, Weinert	Punch drunk
7	A. W.	LW		Asylum
8	В. М.	$\mathbf{H}\mathbf{W}$	Moran, Tunney	Asylum
9	J. G.	$\mathbf{H}\mathbf{W}$	Sharkey, Jeffries,	Asylum
			Fitzsimmons,	
			Johnson	
10	C. S.	MW	******	Asylum
11	J. C.		• • • • • • • • • • • • • • • • • • • •	Drags leg; talks slow; thinks slow
12	J. R.			Punch drunk
13	M. D.			Puneh drunk; almost blind
14	C. C.		*************	Punch drunk
15	T. S.		************	Punch drunk
16	J. S.			Punch drunk
17	R. S.			Punch drunk
18	S. M.			Punch drunk
19	P. J. G.			Punch drunk
20	T. T.			Punch drunk
21	В. М.			Punch drunk
22	J. H.			Punch drunk
23	D. P.			Punch drunk
		-		- ·· -· ···
	_			

the brain. This type of hemorrhage does not occur when the skull is fractured. There is often not even a laceration of the scalp. Cortical laceration and hemorrhage is absent or there may be only a slight amount of thin pia-arachnoid bleeding. While this type of cranial injury was known to a few performing medicolegal autopsies, it has never attracted sufficient clinical attention. We are indebted to Cassasa for first describing it and to Osnato and Giliberti for first calling attention to its clinical importance.

- 2. The mechanical theory advanced by Cassasa offers the best explanation of the production of these hemorrhages. Fat embolism may produce similar hemorrhages in the brain which grossly and microscopically are so alike as to be practically indistinguishable. In such cases the anatomic proof of extensive fat embolism must be sought in the other viscera.
- 3. In a series of 309 consecutive cases of cranial injury coming to autopsy, Martland and Beling found this type of hemorrhage in nine cases, or 2.9 per cent. In six of these cases fat embolism was eliminated as the cause of the hemorrhages, and was not proved in the three remaining cases. They first called attention to the frequency of these hemorrhages in the basal nuclei, especially in and near the corpora striata, and to their rarity in the cortex of the cerebrum and below the tentorium cerebelli. They called them "concussion hemorrhages" because a purely mechanical theory seemed best to explain their production. They spoke of them as "ring hemorrhages" because on microscopic examination they appeared as small rings surrounding the vessel and filling the perivascular space of Virchow-Robin.

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4. It is possible that, in cases of cerebral concussion ending in recovery and mild in nature, the symptoms may be attributed to hydraulic shock to the neurons by distention of the perineuronal spaces. Actual hemorrhages may not occur or may be only few in number.

5. It is easily conceivable also that, after many cranial injuries unassociated with fracture of the skull, the so-called concussion hemorrhages may be fewer and not in such vital places as in the fatal cases. Recovery, therefore, takes place. If this is true there is a purely morphologic lesion as the basis of many cases of post-concussion neuroses and psychoses. A replacement gliosis or even a progressive degenerative lesion may be the late manifestations of these former hemorrhages. It is not surprising, then, that some of these cases will mimic the juvenile and presenile forms of paralysis agitans or the late manifestations of epidemic encephalitis. Especially is this so when the frequent location of the hemorrhages in the corpora striata is recalled.

While the establishment of these facts is of enormous importance to the courts and to labor compensation boards in placing many cases of cranial injuries on a firm pathologic basis, it also will have its disadvantages. A very great field is opened for the so-called expert testimony, in which malingerers and those suffering from various forms of psychoses and neuroses may claim undue compensation. The correct diagnosis during life will always be extremely difficult, as the condition can only be proved by autopsy.

6. The condition of punch drunk has been described. While most of the evidence supporting the existence of this condition is based at this time on the observations of fight fans, promoters and sporting writers, the fact that nearly one half of the fighters who have stayed in the game long enough develop this condition, either in a mild form or a severe and progressive form which often necessitates commitment to an asylum, warrants this report. The condition can no longer be ignored by the medical profession or the public. It is the duty of our profession to establish the existence or nonexistence of punch drunk by preparing accurate statistical data as to its incidence, careful neurologic examinations of fighters thought to be punch drunk, and careful histologic examinations of the brains of those who have died with symptoms simulating the parkinsonian syndrome. The late manifestations of punch drunk will be seen chiefly in the neurologic clinics and asylums, and such material will practically fall to the neuropathologist connected with such institutions.

Punch drunk bears the same relation to multiple concussion hemorrhages as do many of the postconcussion neuroses and psychoses that follow blows or falls on the head.

From the studies of Cassasa, Osnato and Giliberti, and Martland and Beling, it would seem that the older theories of cerebral concussion will have to be discarded. We now have the possibility of a definite type of brain injury explaining the various phases and late manifestations following many cases of cranial injuries.

The following extracts from a copyrighted story which appeared in the New York Daily News, Aug. 3, 1928, are of special interest in connection with the foregoing. In discussing his retirement from the prize ring, Gene Tunney said, in connection with his training for the second Dempsey fight: "I went into a clinch with my head down, something I never do. I plunged forward, and my partner's head came up and butted me over the left eye, cutting and dazing me badly. Then he stepped back and swung his right against my

jaw with every bit of his power. It landed flush and stiffened me where I stood. . . That is the last thing I remembered for two days. They tell me that I finished out the round, knocking the man out." Tunney further stated that it was forty-eight hours before he knew who he was, and not until the seventh round of the Dempsey fight was he entirely normal. In concluding, he said: "From that incident was born my desire to quit the ring forever, the first opportunity that presented itself. . . . But most of all I wanted to leave the game that had threatened my sanity before I met with an accident in a real fight with six ounce gloves that would permanently hurt my brain."

Clinical Notes, Suggestions and New Instruments

PATENT DUCTUS ARTERIOSUS IN A WOMAN IN HER SIXTY-SIXTH YEAR

PAUL D. WHITE, M.D., BOSTON

Patent ductus arteriosus is not rare and its uncomplicated presence has always been believed to be compatible with an active and long life, but recorded instances of old people with the proved condition are very rare. In Dr. Maude Abbott's most recent series of 850 cases of congenital cardiac defects, uncomplicated patent ductus arteriosus is noted as having been found in eighty-four. The range of age was from 2 weeks to 66 years, though it seems fairly certain that the condition may occur even at a much older age than 66.

In 5,000 consecutive autopsies at the Massachusetts General Hospital, patency of the ductus arteriosus was found ninetysix times but in only seven patients over 1 year old; the ages of these seven were 1½, 2, 3, 7, 44, 50 and 55 years, respectively.

of these seven were 1½, 2, 3, 7, 44, 50 and 55 years, respectively. The present case is reported not only because of the age of the patient, 65 years 9 months, which is almost equal to that of the oldest patient in Dr. Abbott's series, but also because the diagnosis was correctly made two years before death. In the older patient (Josefson's case) cited by Dr. Abbott the clinical diagnosis of mitral stenosis was incorrect.

REPORT OF CASE

An unmarried woman, aged 64, was seen in consultation because of circulatory trouble which involved both the heart and the cerebral vessels. She had always been delicate in health from birth but she had not been a blue baby. Unable to play as vigorously as other children because of fatigue, she had lived a quiet life even in her youth. She had, however, never had any serious illness.

The family history was not important, except that her father had suffered from tuberculosis of the hip and one brother had

died of tuberculous meningitis.

It was at the age of 40 that she first was told of any heart trouble, but what it was she did not know. Six months before coming to me for examination she had had a transient left hemiplegia lasting from ten to twelve days and clearing up completely except for a residual increased weakness. Since this hemiplegia she had been in bed off and on.

Her chief complaint at the time of examination was weakness. There were dyspnea, palpitation and precordial oppression at times on excitement but no asthma or clear angina pectoris. There had not been any edema and only rare cough, without

sputum. Otherwise there were no symptoms.

On physical examination the patient appeared small and frail, with flushed cheeks and slight cyanosis of the mucous membranes. The mental condition was clear. There was no clubbing or cyanosis of the fingers, and no paralysis was evident. The lungs were clear and the abdomen was normal. The liver and spleen were not felt. There was no ascites or edema of the

Then 2. Josefson, A.: Offenstehender Ductus Botalli nebst Atherom in den my Asten der Arteria pulmonalis, Nord. med. Ark. New Series 7, number 10, JA3497

Abbott, Maude, in Blumer's Bedside Diagnosis, Philadelphia, W. B. Saunders Company, 1928.
 Josefson, A.: Offenstehender Ductus Botalli nebst Atherom in den

EXHIBIT 53

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REVIEW ARTICLE

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury

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Abstract

Since the 1920s, it has been known that the repetitive brain trauma associated with boxing may produce a progressive neurological deterioration, originally termed dementia pugilistica, and more recently, chronic traumatic encephalopathy (CTE). We review 48 cases of neuropathologically verified CTE recorded in the literature and document the detailed findings of CTE in 3 professional athletes, 1 football player and 2 boxers. Clinically, CTE is associated with memory disturbances, behavioral and personality changes, parkinsonism, and speech and gait abnormalities. Neuropathologically, CTE is characterized by atrophy of the cerebral hemispheres, medial temporal lobe, thalamus, mammillary bodies, and brainstem, with ventricular dilatation and a fenestrated cavum septum pellucidum. Microscopically, there are extensive tauimmunoreactive neurofibrillary tangles, astrocytic tangles, and spindle-shaped and threadlike neurites throughout the brain. The neurofibrillary degeneration of CTE is distinguished from other tauopathies by preferential involvement of the superficial cortical layers, irregular patchy distribution in the frontal and temporal cortices, propensity for sulcal depths, prominent perivascular, periventricular, and subpial distribution, and marked accumulation of tau-immunoreactive astrocytes. Deposition of β-amyloid, most commonly as diffuse plaques, occurs in fewer than half the cases. Chronic traumatic encephalopathy is a neuropathologically distinct slowly progressive tauopathy with a clear environmental etiology.

Key Words: Athletes, Concussion, Dementia, Encephalopathy, Neurodegeneration, Tau protein, Traumatic brain injury.

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INTRODUCTION

During recent years, there has been increasing attention focused on the neurological sequelae of sports-related traumatic brain injury (TBI), particularly concussion. Concussion is a frequent occurrence in contact sports: 1.6 to 3.8 million sports-related concussions occur annually in the United States (1-3). Most sports-related head injury is minor, and although most athletes who have a concussion recover within a few days or weeks, a small number of individuals develop long-lasting or progressive symptoms. This is especially true in cases of repetitive concussion or mild TBI, in which at least 17% of individuals develop chronic traumatic encephalopathy (CTE) (4). The precise incidence of CTE after repetitive head injury is unknown, however, and it is likely much higher. It is also unclear what severity or recurrence of head injury is required to initiate CTE; no well-designed prospective studies have addressed these important public health issues (5-10).

Repetitive closed head injury occurs in a wide variety of contact sports, including football, boxing, wrestling, rugby, hockey, lacrosse, soccer, and skiing. Furthermore, in collision sports, such as football and boxing, players may experience thousands of subconcussive hits during the course of a single season (11, 12). Although the long-term neurological and neuropathologic sequelae associated with repetitive brain injury are best known in boxing, pathologically verified CTE has been reported in professional football players, a professional wrestler, and a soccer player, as well as in epileptics, head bangers, and domestic abuse victims (13-21). Other sports associated with a postconcussive syndrome include hockey, rugby, karate, horse riding, and parachuting (22-25), although the list is almost certainly more inclusive. Furthermore, additional large groups of individuals prone to repetitive head trauma, such as military veterans, may be at risk for CTE.

In this review, we present a summary of the 48 cases of neuropathologically verified CTE in the literature. We also report the clinical and immunocytochemical findings of CTE in 3 retired professional athletes, that is, 1 football player and 2 boxers, ranging in age from 45 to 80 years. Although the cases previously reported in the literature detailed some of the characteristic gross and histological features of CTE, the spectrum of unique regionally specific immunocytochemical abnormalities of phosphorylated tau

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that occur in this disorder has not been previously described. We demonstrate that although CTE shares many features of other neurodegenerative disorders, including Alzheimer disease (AD), progressive supranuclear palsy (PSP), postence-phalitic parkinsonism, and the amyotrophic lateral sclerosis/Parkinson-dementia complex of Guam (ALS/PDC), CTE is a neuropathologically distinct progressive tauopathy with a clear environmental etiology.

CLINICAL AND DEMOGRAPHIC FEATURES OF CTE

The concept of CTE was first introduced by Martland (26) in 1928, who introduced the term punch-drunk to a symptom complex that seemed to be the result of repeated sublethal blows to the head. This syndrome, long recognized in professional boxers, was termed dementia pugilistica by Millspaugh (27) and the psychopathic deterioration of pugilists by Courville (28). The symptoms of CTE are insidious, first manifested by deteriorations in attention, concentration, and memory, as well as disorientation and confusion, and occasionally accompanied by dizziness and headaches. With progressive deterioration, additional symptoms, such as lack of insight, poor judgment, and overt dementia, become manifest. Severe cases are accompanied by a progressive slowing of muscular movements, a staggered propulsive gait, masked facies, impeded speech, tremors, vertigo, and deafness (27). Corsellis et al (29) described 3 stages of clinical deterioration as follows. The first stage is characterized by affective disturbances and psychotic symptoms. Social instability, erratic behavior, memory loss, and initial symptoms of Parkinson disease appear during the second stage. The third stage consists of general cognitive dysfunction progressing to dementia and is often accompanied by full-blown parkinsonism, as well as speech and gait abnormalities. Other symptoms include dysarthria, dysphagia, and ocular abnormalities, such as ptosis (29). The severity of the disorder seems to correlate with the length of time engaged in the sport and the number of traumatic injuries, although whether a single TBI can trigger the onset of CTE remains a matter of speculation.

Of the 51 neuropathologically confirmed cases of CTE, 46 (90%) occurred in athletes. The athletes included 39 boxers (85%) who fought as amateurs and as professionals for varying lengths of time (range, 4-25 years; mean, 14.4 years), 5 football players (11%) whose playing time ranged between 14 and 23 years (mean, 18.4 years; SD, 3.9), 1 professional wrestler, and 1 soccer player. The athletes began their respective sports at young ages, that is, between 11 and 19 years (mean, 15.4 years; SD, 2.2) (Tables 1 and 2). The first symptoms of CTE were noticed at ages ranging from 25 to 76 years (mean, 42.8 years; SD, 12.7). One third were symptomatic at the time of their retirement from the sport, and half were symptomatic within 4 years of stopping play. Common presenting symptoms included memory loss, irritability, outbursts of aggressive or violent behavior, confusion, speech abnormalities, cognitive decline, gait abnormalities, unsteadiness, headaches, slurred speech, and parkinsonism. In 14 cases (30%), there was a prominent

mood disturbance, usually depression (28%); 1 boxer was described as having a "euphoric dementia" (31); another boxer was described as manic-depressive (35); and a football player was considered "bipolar" (40). In most of the reported cases, the disease slowly progressed for several decades (range, 2–46 years; mean, 18.6 years; SD, 12.6), with increasing abnormalities in behavior and personality, memory loss, cognitive decline, and visuospatial difficulties. Movement abnormalities were eventually found in 41.2% subjects consisting of parkinsonism; staggered, slowed, or shuffled gait; slowed, slurred, or dysarthric speech; ataxia; ocular abnormalities; and dysphagia. As Critchley (42) noted in 1957, "once established, it not only does not permit reversibility, but ordinarily advances steadily, even though the boxer has retired from the ring."

CTE in Football Players

Five football players, including our Case A, had neuropathologically verified CTE at autopsy. All died suddenly in middle age (age at death, 36-50 years; mean, 44.0 years; SD, 5.0) and were younger at the time of death compared with boxers with CTE (age at death, 23-91 years; mean, 60.0 years; SD, 15.2). The duration of symptomatic illness was also shorter in the football players (range, 3-10 years; mean, 6.0 years; SD, 2.9) compared with the boxers (range, 5-46 years; mean, 20.6 years; SD, 12.3). All 5 football players played similar positions: 3 were offensive linemen, one was a defensive lineman, and the other was a linebacker. In the football players, the most common symptoms were mood disorder (mainly depression), memory loss, paranoia, and poor insight or judgment (each found in 80%), outbursts of anger or aggression, irritability, and apathy (each found in 60%), confusion, reduced concentration, agitation, or hyperreligiosity (each found in 40%). Furthermore, 4 of the 5 experienced tragic deaths, that is, 2 from suicide (16, 17), one during a high-speed police chase (40), and another from an accidental gunshot while cleaning his gun (Case A). Case A exemplifies these clinical features.

Case A

A 45-year-old right-handed white man died unexpectedly as a result of an accidental gunshot wound to the chest while he was cleaning a gun. He was a retired professional football player who played football in high school, 3 years of college, and 10 years in the National Football League as a linebacker. According to his wife, he was concussed 3 times during his college football years and at least 8 times during his National Football League career; however, only 1 concussion was medically confirmed. He was never formally diagnosed as having postconcussive syndrome and never sought medical attention for residual cognitive or behavioral difficulties. There was no history of ever losing consciousness for more than a few seconds, and he never required being carried off the field or hospitalization.

At age 40 years, his family began to notice minor impairments in his short-term memory, attention, concentration, organization, planning, problem solving, judgment, and ability to juggle more than one task at a time. His spatial abilities were mildly impaired, and his language was unaffected.

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Case No.	Reference	Sex	Sport/Activity	Age Sport Begun, years	Years of Play	Age at Onset Symptoms, years	Interval Between Retirement and Symptoms, years	Interval Between Symptom Onset and Death, years	Age at Death, years	ApoE Genotype
1	30	M	Boxing	17	11	38	10	13	51	
2	31	M	Boxing	15	14	36	6	12	48	
3	32	M	Boxing	14	10	46	10	7	53	
4	32	M	Boxing	18	6	48	24	10	58	
5	28	M	Boxing		4				49	
6	33	M	Boxing							
7	33	M	Boxing							
8	34	M	Boxing	16	7	25	1	33	58	
9	35	M	Boxing	12	12	30	6			
10	35	M	Boxing	15	20	36	0	10	46	
11	35	M	Boxing	19	12	31	0	15	46	
12	35	M	Boxing	16	16	40	8	5	45	
13	35	M	Boxing	15	13	28	0	16	44	
14	35	M	Boxing	12	12		4		28	
15	29	M	Boxing	11	14	25	0	38	63	
16	29	M	Boxing		20	50	20	27	77	
17	29	M	Boxing	16	14	30	0	33	63	
18	29	M	Boxing	15	25	35	0	34	69	
19	29	M	Boxing	18	18	36	0	25	61	
20	29	M	Boxing	13	25	37	0	46	83	
21	29	M	Boxing	16	20	54	18	8	62	
22	29	M	Boxing	17	23	60	20	11	71	
23	29	M	Boxing		>10	31	0	41	72	
24	29	M	Boxing			40		27	67	
25	29	M	Boxing			48		19	67	
26	29	M	Boxing	14	16	43	4	14	57	
27	29	M	Boxing	18	10	93		1.4	61	
28	29	M	Boxing	10	10				91	
29	29	M	Boxing						58	
30	18	F	Physical abuse						76	
31	14	F	Autistic head banging						24	
32	36	M	A STATE OF THE PROPERTY OF THE		>25				63	
33	36	M	Boxing Boxing		>25				69	
34	19	M	Circus clown		15					
35	15				>11	41	27	30	33	
36		M	Boxing	- 20		61	37	10	71	20.4
37	13, 37	M	Boxing	11	12		n .		23	€3/€4
38	13	M	Boxing	16	5		0		28	
		M	Head banging						28	
39	13	M	Epilepsy						27	200
40	13	M	Soccer			24			23	€3/€3
41	38	M	Boxing		10	64			67	€3/ε4
42	39	M	Boxing	.72		76			78	2.3
43	17	M	Football	16	22	and the second	-	400	50	ε3/ε3
44	16	M	Football	18	14	35	2	10	45	€3/€3
45	21	M	Football	15	23	38	0	6	44	€3/€4
46	20	M	Wrestling	18	22	38	0	2	40	€3/€3
47	40	M	Football	16	17	36	3	3	36	
48	41	M	Boxing	16	17	58		13	61	€3/€3
49	Case A	M	Football	16	16	40	9	5	45	€4/€4
50	Case B	M	Boxing	17	5	63	33	17	80	€3/€4
51	Case C	M	Boxing	11	22	58	25	15	73	ε3/ε3

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Case No.	Initial Symptoms	I. Personality/Behavior Change	Dysphoria	Irritability	Confusion	Agitation	Paranoia
1	Memory, speech	x				x	
2	Euphoria, dementia	x	x				
3		x		x			×
4	Memory, confusion	×	x	x	x		
5	Memory, confusion	x			×		
6							
7	Company of the Compan						
8	Cognitive decline, hemiparesis	x	X	x	×		x
9	Manic-depressive psychosis	x	x				
10	Headaches	x	×		X		x
11	Headaches	x	x		X		
12	Slurred speech, gait change	x	X		x		
13	Punchy, unsteady						
14	ore a serior serior serior						
15	Violent outbursts	x		x	5		
16	Staggered gait, slowed speech Confusion, falls	x		x	x		
17 18	Unsteadiness	x		x	X	X	×
19	Irritability, memory loss, aggression	3					
20	Gait, speech	x		x			
21	Dysphoria, violence	x			-		×
22	Ataxia, falls, weakness	x			x		
23	Tremor, slurred speech	x					
24	Memory loss	x			x	x	×
25	Confusion	x			x	2	^
26	Speech, delirium	x			- 2		x
27	None	Α.			X		
28	Aggression	x					
29	None	~					
30	710/10						
31							
32		x	x				
33		x	x				
34		x					
35		2					
36							
37	Paranoid schizophrenia						
38							
39							
40							
41	Cognitive decline, ALS-like syndrome	x		x	x	x	x
42	Cognitive decline, parkinsonism						
43	Memory, dysphoria	x	X				
44	Depression, erratic	x	x	x		x	x
45	Headaches, poor decisions	×	x				x
46	Depression, violent	x	x				
47	Bipolar disorder	x	×	x	x	×	x
48	Memory loss						
A*	Memory, confusion	x	x	x	×		x
B*	Disorientation, confusion	x		x	x	x	x
C*	Memory	x	x	x	x	x.	x

^{*}New Cases A, B, and C of this series.

x, clinical feature was noted as present; blank, clinical feature was not mentioned. ALS, amyotrophic lateral sclerosis.

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TABLE 2. (Con		Dean Yestehal			II Comette			
Reduced Concentration	Aggression/ Violence	Poor Insight/ Judgment	Apathy	Hypersexuality	II. Somatic Symptoms	Headache	Dizziness	Insomni
	X	×						
	×				x	×		
×	x				×	x		x
X.	x				x	x		x
	×							
	X							
	×							
	x							
	×			x	x	×		
	x							
	x							
	x							
	x							
	x							
	x							
		×						
	x							
x	x	×						
	x							
	Q.	x						
Α.	x	x x	x		x	x		
	x x				x	x		
x	x	x x x	x					
		2						
x x	x x	x						
x	x	x	x		x		x	

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Case No.	Deafness	Epilepsy	III. Cognitive Changes	Memory Loss	Dementia	Visuospatial Abnormalities	IV. Movement Abnormalities	Parkinsonism	Decreased Facial Movement
1			x	х	х		x	x	
2		x	x	x	x		x	x	
3			×	x			x		
4			x	x	x				
5			x						
6									
7									
8		x	x	X	x		x	X	X
9									
10									
11			x	x			x	x	
12			x	x					
13			x						
14							x	x	
15			x	x			x	×	
16			x	x	x		x		
17			x	x				×	×
18			x	x	x		x	×	
19			x	x					
20			x	x			x	x	
21			x	x	x		×		
22			x				x	x	
23			×	x	x		×	×	x.
24			x	x	x				
25			x	x	x				
26			x	x	x		x	x	
27									
28									
29									
30									
31									
32			×	x			x	x	x
33			x	x			x	x	×
34			x	x	x				
35			x	x	x				
36									
37									
38									
39									
40									
41			x	x	x		x	×	x
42			×	x	x		×	x	
43			x x x	x x	x x x		x	* * *	
44									
45			x	x					
46			x	x x					
47			x	x	x				
48			x	x	- 3	x			
A*			x x	x		x			
B*			×	x	x	x x	x		
C*			x	x	x	x	x	x	x

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lowed Movements	Tremor	Rigidity	Falls	Ocular Abnormalities	Ptosis	Reduced Upgaze	Gait Problems	Staggered
x								
	X			X.		x	*	
			x.					
×								
				ĸ			x	
							×	
							x	×
							×	x
	x		x	x	x		X	×
	x	x	x				×	×
x		x					x	
							x	x
			x				x	
	x x		x				X	
	x	x	x				x	
x								
	x						×	
	x x						×	
							×	
							×	
			x					
			x				×	x
	x			x		x	x	

Case No.	Slowed	Shuffled	Ataxia	Reduced Coordination	Speech Changes	Slowed	Slurred	Dysarthria	Dysphagia	Spasticity
1	110000	, san taken			x	x				
2			x							x
3			x							x
4										
5 6 7 8										
6					x					
7		x						*		x
							- 2	4.3		
9			x		x x		x x	x		
10					×		X			
11				x-	X	x				
12 13				x	x					
14			x		x					
15			×		x	x	x			
16			x		x	x x	x	x	x	x
17		x	×		x		x	×		x
18										
19	x	×	x		x		x	x		
20			x							
21			x		x					
22			×				x	x		
23								×		
24										
25					x	×	х			
26										
27										
28										
29										
30										
31					x			x		
32					x			x		
33			x							
34										
35										
36										
37										
38										
39 40										x
41					x					x
42										
43										
44										
44 45										
46										
47										
48										
A*										
B*					x x		x			
C*	x	x			x		x			

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He repeatedly asked the same questions over and over, he did not recall why he went to the store unless he had a list, and he would ask to rent a movie that he had already seen. These symptoms gradually increased and became pronounced by the end of his life 5 years later. Using a modification of the Family Version of the Cognitive Difficulties Scale (43, 44), he had a moderate amount of cognitive difficulties. On a modified AD8 informant interview for dementia, he received a total score of 4, which indicated "cognitive impairment is likely to be present" (45). By contrast, the Functional Activities Questionnaire (46), an informant-based measure of instrumental activities of daily living, did not indicate significant functional dependence despite his difficulty in assembling tax records, shopping alone, and understanding television (total Functional Activities Questionnaire score, 3). Moreover, he continued to perform his job as a hunting and fishing guide in a satisfactory manner.

Toward the end of his life, he tended to become angry and verbally aggressive over insignificant issues and was more emotionally labile. He also began to consume more alcohol but did not show other signs or symptoms of depression. He had no significant psychiatric history, and he had never taken performance-enhancing or illicit drugs. His family history was negative for dementia and psychiatric illness.

CTE in Boxers

Boxing is the most frequent sport associated with CTE, and disease duration is the longest in boxers, with case reports of individuals living for 33, 34, 38, 41, and 46 years with smoldering, yet symptomatic, disease (29). Boxers with long-standing CTE are frequently demented (46%) and may be misdiagnosed clinically as AD (47), as occurred in Cases 2 and 3.

Case B

An 80-year-old African American/American Indian man was first noted to have difficulty remembering things in his mid-20s. He began boxing when he was 17 years old, quickly rose to professional ranks, and fought professionally for 5 years until he retired at age 22 years. He had a mild head injury in his early teenaged years while moving farm equipment, although he did not lose consciousness or experience any permanent disability. By his mid-30s, he had brief occasional episodes of confusion and a tendency to fall. His wife attributed his occasional forgetfulness, falls, and confusion to being mildly "punch-drunk." His symptoms remained more or less stable during the following 4 decades except for an increased tendency to become disoriented when traveling to unfamiliar places. By age 70 years, he got lost driving on familiar roads; he became increasingly confused and disoriented and did not recognize his daughter. By age 78 years, he was paranoid, his memory loss had increased, his gait was unsteady, his speech slowed, and he frequently fell. He was easily agitated and required multiple hospitalizations for aggressive behaviors. He died at age 80 years of complications of septic shock.

He had a period of alcohol abuse as a young adult but was abstinent for the last 40 years of his life. He smoked cigarettes for 20 years. He was employed as a roofer for most

of his life and was in excellent physical condition, running miles and doing daily calisthenics. He had no history of depression or anxiety and was generally pleasant and eventempered. His family history was positive for a paternal grandfather with a history of cognitive decline and a brother with AD. Cerebral computerized axial tomography performed 2 and 3 years before death revealed progressive cerebral and cerebellar atrophy and mild ventricular enlargement.

Case C

A 73-year-old white man began boxing at the age of 11 years and fought as an amateur boxer for 9 years and as a professional boxer for 13 years. He fought a total of 48 professional bouts, accumulating 2 world championships before retiring at the age of 33 years. In his late 50s, he became forgetful with mood swings and restlessness. He changed from his normally happy easy-going self to become apathetic, socially withdrawn, paranoid, irritable, and sometimes violently agitated. During the next 2 years, he began to confuse close relatives and developed increasing anxiety, aggression, and agitation; on occasion, he was verbally abusive toward his wife and tried to strike her. He required neuroleptics for control of his behavior. The following year, he had episodes of dizziness, which was suspected to be vertigo, and resulted in a hospital admission. Neurological examination found him to be disoriented, inattentive, with very poor immediate and remote memory, and impaired visuospatial skills. Neuropsychological testing showed deficits in all cognitive domains, including executive functioning, attention, language, visuospatial abilities, and profound deficits in learning and memory. Computed tomographic scan and magnetic resonance imaging (MRI) showed generalized cortical atrophy, enlargement of the cerebral ventricles, cavum septum pellucidum, and a right globus pallidus lacuna. An electroencephalogram, an MR angiogram, and a carotid ultrasound were normal. He smoked and drank alcohol occasionally until his early 50s. A first cousin developed dementia in her early 50s, and 3 uncles and 1 aunt (of 11 children) were

During the following 2 years, he continued to decline in all cognitive domains. He frequently fell and developed a tremor of his left hand. Repeat neuropsychological testing at age 67 years revealed further global deficits, again with prominent impairments in memory. By age 70 years, he had severe swallowing difficulties, diminished upgaze, masked facies, garbled speech, and a slow shuffling gait. Mini-Mental Status Examination several months before death was 7 out of 30. He died at the age of 73 years of complications of pneumonia.

CTE in Other Sports and Activities

Other sports associated with neuropathologically verified CTE are professional wrestling (20) and soccer (13). The first known case of CTE in a professional wrestler involved a 40-year-old white man who began professional wrestling at age 18 years and wrestled for the next 22 years (20). He was known for his rough aggressive style and had experienced numerous concussions and a cervical fracture during his career. At age 36 years, he began to experience problems in

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Case No.	Brain Weight, g	Thickened Leptomeninges	Atherosclerosis	Arteriolosclerosis	Cerebral Atrophy	Frontal Lobe	Parietal Lobe	Temporal Lobe	Occipita Lobe
1		++	0	++	+				
2					+				
3	(Biopsy)								
4						111			
5	1,120	+	0			+	+		
6									
7									
8	1,180				+				
9		+	++	++	+	7			
10		+	++:	++					
11		+	+						
12		+	+						
13		*	+						
14	1 210	+							
15	1,310	++	+	1-7	1.60	· ·		+++	
16	960		+	++	+++	111		111	
17 18	1,260 1,205	+			4	+			
19	1,095	+				4+		++	
20	1,300	+				0	0	0	0
21	1,090	+				U	U	· ·	U
22	1,040					111		+++	
23	1,435					200			
24	1,095								
25	1,030								
26	1,050								
27	950					+			
28	1,395					7			
29	1,070								
30						+			
31									
32						+			
33									
34	1,833		0						
35						+	+	+	
36									
37									
38									
39	(Lobectomy)								
40									
41						+		+	
42								+	
43	1,565					0	0	0	0
44									
45	1,535					0	0	0	0
46	1,510					0	0	0	0
47									
48						++		++	
A*	(Fragments)	0	0	0	0	0	0	0	0
B* C*	1,360 1,220	0 +	0	++	+++	+++	+	+	0 +

^{*}New Cases A, B, and C of this series.

0. feature not present; +, mild; ++, moderate; +++, severe; blank, feature was not mentioned.

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Chronic Traumatic Encephalopathy in Athletes

ATT VICE A	Entorhinal	1000	Mammillary Bodies	Thalamus/	-200	time discontinu	Olfactory Bulb	Corpus Callosur
Hippocampus	Cortex	Amygdala	Bodies	Hypothalamus	Brainstem	Cerebellum	Bulb	Callosur
			+	4	#			
			+	+	+	+		. +
			+	+	+	+		
				+	+	+	+	+
				+		+	+	+
					+	+		+
					+			
				+	4			
					+			+
			+					+
							1.0	
							+	
				+		+++		++
0	0	0		14				
+++	+++	+++	++	++	0	0	0 +	+
	3.3-4		1.0	- 11	, a	, U		7

his marriage, with periods of depression and lapses of memory. During his 40th year, he had episodes of violent behavior; he ultimately killed his wife and son and committed suicide. He was believed to have used anabolic steroids and prescription narcotics. His medical history included a motor vehicle accident at age 6 years requiring 3 days of hospitalization for mild TBI without known neurological sequelae.

Geddes and colleagues (13) reported finding mild changes of CTE in a 23-year-old amateur soccer player who regularly "headed" the ball while playing and had a history of a single severe head injury. Williams and Tannenberg (19) reported the findings of CTE in a 33-year-old achondroplastic dwarf, with a long history of alcohol abuse, who worked for 15 years as a clown in a circus. He had been knocked unconscious "a dozen times" and participated in dwarf-throwing events.

PATHOLOGICAL FEATURES OF CTE

Gross Pathology

In their comprehensive description of the pathology, Corsellis and colleagues (29) summarized the most common gross neuropathologic findings including 1) a reduction in brain weight, 2) enlargement of the lateral and third ventricles, 3) thinning of the corpus callosum, 4) cavum septum pellucidum with fenestrations, and 5) scarring and neuronal loss of the cerebellar tonsils. The reduction in brain weight is generally mild (mean, 1261 g; range, 950-1,833 g) and associated with atrophy of the frontal lobe (36%), temporal lobe (31%), parietal lobe (22%), and less frequently, occipital lobe (3%) (Tables 3-6). With increasing severity of the disease, atrophy of the hippocampus, entorhinal cortex, and amygdala may become marked. The lateral ventricles (53%) and III ventricles (29%) are frequently dilated; rarely, there is dilation of the IV ventricle (4%). Cavum septum pellucidum is often present (69%), usually with fenestrations (49%). Other common gross features include pallor of the substantia nigra and locus caeruleus, atrophy of the olfactory bulbs, thalamus, mammillary bodies, brainstem, and cerebellum, and thinning of the corpus callosum. Many of these gross pathological features were found in our Cases B and C.

Case B

The brain weighed 1,360 g. There was a mild yellow-brown discoloration in the leptomeninges over the temporal poles. There was mild atrophy of the frontal, parietal, and temporal lobes, most pronounced in the temporal pole. The floor of the hypothalamus was thinned and translucent, and the mammillary bodies were atrophic. The medial thalamus was atrophic and concave. The frontal, temporal, and occipital horns of the lateral and third ventricles were enlarged, with a 0.5-cm cavum septum pellucidum. The corpus callosum was thinned in its midportion. The anterior hippocampus, amygdala, and entorhinal cortex were severely atrophic. By contrast, the posterior hippocampus was only mildly atrophic. The substantia nigra and locus caeruleus were markedly pale.

Case C

The brain weighed 1,220 g. There was moderate atrophy of the frontal, parietal, and temporal lobes, most pronounced in the temporal pole. The floor of the hypothalamus was markedly thinned, and the mammillary bodies were atrophic. The corpus callosum was thinned, most prominently in its anterior portion. There was a large cavum septum pellucidum (0.8 cm) with fenestrations. The frontal and temporal horns of the lateral ventricles and the third ventricle were moderately enlarged. The entorhinal cortex, hippocampus, and amygdala were markedly atrophic throughout their entire extent. The medial thalamus was atrophic and concave. The perivascular spaces of the temporal and frontal white matter were prominent. A 1.0-cm lacuna was present in the internal segment of the right globus pallidus. There was severe pallor of the substantia nigra and locus caeruleus, with discoloration and atrophy of the frontopontine fibers in the cerebral peduncle.

See the appendix for methods of analysis for Cases A to C.

Microscopic Pathology

Neuronal Loss

A few reports in the literature (Cases 3, 4, 10, 12, 14, 29; Table 5) described neuronal loss and gliosis in the hippocampus, substantia nigra, and cerebral cortex without appreciable neurofibrillary pathology. Neuronal loss and gliosis most commonly accompany neurofibrillary degeneration, however, and are pronounced in the hippocampus, particularly the CA1 and subiculum, the entorhinal cortex, and amygdala. If the disease is advanced, neuronal loss is also found in the subcallosal and insular cortex and to a lesser degree in the frontal and temporal cortex. Other areas of neuronal loss and gliosis include the mammillary bodies, medial thalamus, substantia nigra, locus caeruleus, and nucleus accumbens. In Cases B and C, the cerebral cortex showed mild neuronal loss in the insular and septal cortices and moderate neuronal loss in the entorhinal cortex, amygdala, medial thalamus, mammillary bodies, substantia nigra pars compacta and pars reticulata, and to a lesser extent, locus caeruleus. In Case B. CA1 of the hippocampus showed moderate loss of neurons, and in Case C, CA1 and the subiculum of the hippocampus showed severe neuronal loss and gliosis.

Tau Deposition

Neurofibrillary tangles (NFTs), astrocytic tangles, and dotlike and spindle-shaped neuropil neurites (NNs) are common in the dorsolateral frontal, subcallosal, insular, temporal, dorsolateral parietal, and inferior occipital cortices. The tau-immunoreactive neurofibrillary pathology is characteristically irregular in distribution with multifocal patches of dense NFTs in the superficial cortical layers, often in a perivascular arrangement. This superficial distribution of neocortical NFTs was originally described by Hof and colleagues (47), who noted that the NFTs in CTE were preferentially distributed in layer II and the upper third of layer III in neocortical areas and generally more dense than in AD.

Geddes and colleagues (13, 37) drew attention to the perivascular distribution of NFTs in their description of the

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Case No.	II Ventricle Enlarged	III Ventricle Enlarged	IV Ventricle Enlarged	Cavum Septum	Fenestrations	SN Pallor	LC Pallo
1	+	+					91,791 6,5910
2	+			+			
3							
4	+++						
5	+	+					
6				+			
7				+			
8				+		111	
9	+			+	+		
10	+			+	+		
1	+			+			+
2	+			+			
13	+			+	+		
14	+			+			
15	++	++		411	+	++	
6	+++	+11+	+++	111	+	++	
7	++	++		++	+	+++	
8	++	4+	2.	+	+	+++	
9	++	++	+	+++	+	+	
20	++	1.1		++	+	+++	
22	++	++		++	-		
23	++	++	+	++	+	100	
4	116	+++		+++		+++	
5	++	144		+++	+		
.6	+			+	- T		
27	++	++		++	+		
28	++	++		++			
.9				14	+		
30				+++	+		
11				111			
2				4	+		
3							
14	+++	+++			+		
5					+		
6				0	0	0	
17				0	0	0	
8				0	0	0	
9							
0				0	0	0	
1				C+0		++	++
2				+			
3						+	
4							
5				+			
6							
7							
8	++			+	4		
*	100	+				0	0
3*	+			+	+	+++	+++
. W	++	**		++	+	+++	+++

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Case No.	Frontal Cortex	Parietal Cortex	Temporal Cortex	Occipital Cortex	Hippocampus	Entorhinal Cortex	Amygdala	Cerebellun
1								
2								
3	1++	111	+++					
4	+++	+++	+++					
5								
6								
7								
8								
9								
10								
1								
2								
13								
14	+							
		+++	111					
6	111	737	345					
18								
19								
20	*	+	+	1				
21	4							
22	+	+	4	+				
23	+	+	+	+				
24		3						
25								
26	+++	+++	+++	+++				
27			-3,5					
28								
29								
30								
31								
32								
33								
34								
35								
36								
37								
38								
39								
40								
41								
42								
13								
14								
15								
46								
47								
48	++	++	++	++	**		1.5	
A*	0	0	0	0	+	*	+	
B*	+	*	+	+	++	11	++	
2*	++	++	++	++	+++	+++	+++	

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100						NFT					
Case No.	Frontal	Parietal	Temporal	Occipital	Thalamus	Hypothalamus	Septal Nuclei	Globus Pallidus	Caudate/ Putamen	Nucleus Basalis of Meynert	Mammillar Bodies
1	+	+	+	*							
2	+	+	+		+	+					
3											
4											
5	+	+	+								
6	+	+	+								
7	+	+	+								
8	+		+	#							
9											
10		- 11									
11	+	+	+								
13	+	+	+								
14	7	7	7								
15	+										
16	+++	+++	+++								
17	+	+	+								
18	+++		+++								
19	+++	+++	111	+++							
20	+	+	+								
21	+	+	+	+							
22	++	++	++	++							
23	++	++	++	++							
24			+								
25			+								
26	+++	***	111	+++							
27				- 10							
28	+	+	+	+							
29	200	1.0	1								
30 31	++	++	+								
32	+		+							- 4	
33	+		+							+	
34			+								
35											
36			+								
37			+								
38			+								
39			+								
40			+								
41	++		+					++	++		
42	+		+					-			
43	+	+	+								
44	+	+	+								
45	+++		+++	++	+				+		++
46	+	+	+					+	+		
47											
48	++	++	++	0							
A*	+1+	++	+++	++	+	111	+++	0	+	+++	1111
B*	+++	+++	+++	++	++	+++	+++	+	++	+++	+111
C*	+++	+++	+++	++	+++	***	+++	+	++	+++	+++

^{*}New Cases A, B, and C of this series.

^{0,} feature not present; +, mild; ++, moderate; +++, severe; blank, feature was not mentioned.

Aβ, β-amyloid; LC, locus caeruleus; NFT, neurofibrillary tangles; SN, substantia nigra; SP, senile plaques.

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					NFT							
Case No.	Hippocampus	Entorhinal Cortex	Amygdala	Periventricular Gray	Midbrain Tegmentum	SN	LC	Basis Pontis	Medulla	Inferior Olive	Red Nucleus	Cranial Nerves 3, Nuclei
1	111											
2	1.1.1					+++						
1												
5												
	3++	+11	+++	+++	+++	+++	+++					
)												
1												
5												
7												
3												
)												
2												
3												
4												
5												
6												
7												
8												
9												
0	+					+						
1												
2						+	+					
3						+						
4	4.											
5	nan-			+		+	+					+
5	0			+								
7	0											
3	0											
9	0											
)	0											
1	+++											
2	+++											
3	0											
4	++	++				+	+	+	*			
5	++	++	++	+	+	++	++	111	++			
5						+	+					
7												
3	+++					+	+					
•	++	+++	++	+	+	++						
*	+++	+++	+++	++	+.+	+++	+++	+	+	+	+	+
*	+11	3-1-1	+++	++	++	+++	111	++	++	++	++	++

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TABLE 6. (Co		T			Аβ		_			
Cranial Nerve 12 Nucleus	Spinal Cord	Cerebellar Dentate	Olfactory Bulb	Diffuse Plaques	Neuritic Plaques	Congophilic Angiopathy	NFT Only	NFT + SP	SP Only	No NFT/No SI
				111	++	++		+++		134.314.416.41
							+++			
										+
										+
							*			
							+			
							+			
				+	+				+	
				0	0					+
				0	0		+			
				0	0					+
				0	0		+			
				0 +	0			X		+
				+				+		
				+				+		
				+				+		
				+				+		
				+	+			+		
				+	+			+		
				+				+		
				+				+		
				+				+		
				+				+		
				++	++			+		
				+	+			+		
										+
				+	+			+ +		
				+++	++			+		
				0	0	0				
				0	0	0				
				+++	+	4.		+		
				77	++	++	+	+		
							+			
							+			
							+			
							+			
	+++			+	+			+		
							+			
				+				#		
		4444		4	- "		4			
		++++		+	+		+			
				0						
		0	++	0	0	0				
0	.+.	+	+++	++	+	0		+		
+++	++	++	+++	0	0	0	+			

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neuropathologic alterations in the brain and frontal lobectomy specimens of 5 young men, ranging in age from 23 to 28 years. The 5 cases included 2 boxers, a soccer player, a person described as "mentally subnormal" with a long history of head banging, and a patient with epilepsy who frequently hit his head during seizures. Microscopically, all the brains showed argyrophilic tau-positive neocortical NFTs, strikingly arranged in groups around small intracortical blood vessels, associated with neuropil threads and granular tau-positive neurons. There were also NFTs along the basal surfaces of the brain, usually at the depths of sulci. The hippocampi of the 4 autopsy cases were normal.

In CTE, tau-immunoreactive protoplasmic astrocytes are interspersed throughout the superficial cortical layers appearing as plaquelike accumulations composed of primarily globular neurites. The corpus callosum and subcortical white matter of the cortex show NNs and fibrillar astrocytic tangles. The U-fibers are prominently involved. Subcortical white matter structures such as the extreme and external capsule, anterior and posterior commissures, thalamic fasciculus, and fornix also show NNs and astrocytic tangles.

Dense NFTs, ghost tangles, and astrocytic tangles are found in the olfactory bulbs, hippocampus, entorhinal cortex, and amygdala, often in greater density than is found in AD. Abundant NFTs and astrocytic tangles are also found in the thalamus, hypothalamus, mammillary bodies, nucleus basalis of Meynert, medial geniculate, substantia nigra (pars compacta more than the pars reticulata), locus caeruleus, superior colliculus, periaqueductal gray, medial lemniscus, oculomotor nucleus, trochlear nucleus, ventral tegmental area, dorsal and median raphe, trigeminal motor nucleus, pontine nuclei, hypoglossal nucleus, dorsal motor nucleus of the vagus, inferior olives, and reticular formation. The nucleus accumbens is usually moderately affected; the globus pallidus, caudate, and putamen are less involved. In the brainstem and spinal cord, midline white matter tracts show dense astrocytic tangles especially around small capillaries. Fibrillar astrocytic tangles are also common in the subpial and periventricular zones. Neurons in the spinal cord gray matter contain NFTs, and astrocytic tangles are frequent in the ventral gray matter. This unique pattern of tau-immunoreactive pathology was found in all 3 of our cases, with increasing severity from Case A to Case C.

Case A

Neurofibrillary tangles immunopositive for tau epitopes (Appendix) were prominent in the inferior frontal, superior frontal, subcallosal, insular, temporal, and inferior parietotemporal cortices (Fig. 1). Primary visual cortex showed no NFTs; anterior and posterior cingulate cortex showed only scant NFTs. Neurofibrillary tangles occurred in irregular patches, often greatest at the sulcal depths (Fig. 2). Tau-positive fibrillar astrocytes ("astrocytic tangles") were prominent in foci, especially in subpial regions and around small blood vessels (Figs. 2, 3). Neurofibrillary tangles were especially numerous in cortical laminae II and III, where a prominent perivascular distribution of neuronal NFTs and fibrillar astrocytic tangles was evident (Fig. 3). Although some neuronal NFTs showed multiple tau-positive perisomatic processes, most neuronal NFTs were morphologically similar to those found in AD. In the cortex, there were many tau-positive astrocytes bearing a corona of tau-positive processes. These tau-positive protoplasmic astrocytes were similar in appearance to the astrocytic plaques of corticobasal degeneration, except that the perikaryon was often tau positive (Fig. 3).

Neuropil neurites and astrocytic tangles were abundant in the frontal and temporal white matter (Fig. 3). Neuropil neurites were often dotlike and spindle-shaped, in addition to thread-like forms similar to those found in AD. The hippocampus, entorhinal, and transentorhinal cortex contained dense NFTs, ghost tangles, and NNs, including many ghost tangles in CA1 and subiculum; NFTs were denser in the anterior hippocampus compared with the posterior hippocampus. The amygdala showed dense tau immunoreactivity, including NFTs, astrocytic tangles, and NNs (Fig. 4). Neurofibrillary tangles were most frequent in the lateral nuclear group of the amygdala.

The nucleus basalis of Meynert, hypothalamic nuclei, septal nuclei, fornix, and lateral mammillary bodies showed dense NFTs and astrocytic tangles. Neurofibrillary tangles and astrocytic tangles were also found in the olfactory bulb, thalamus, caudate, and putamen. The globus pallidus and



FIGURE 1. Case A. Whole-mount 50-μm coronal sections immunostained for tau with monoclonal antibody AT8 and counterstained with cresyl violet showing irregular patchy deposition of phosphorylated tau protein in frontal, subcallosal, insular, temporal, and parietal cortices and the medial temporal lobe.

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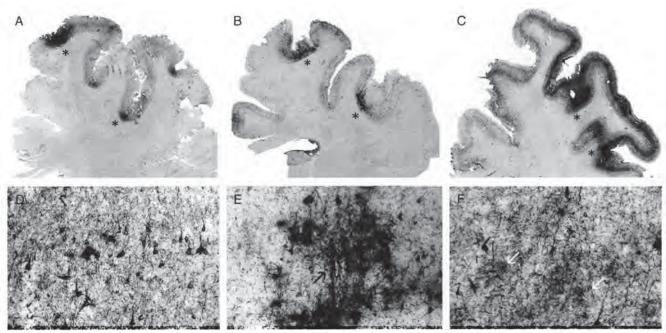


FIGURE 2. (A–C) Whole-mount 50-μm coronal sections of superior frontal cortex from Case A (A), Case B (B), and Case C (C) immunostained for tau with monoclonal antibody CP-13 showing extensive immunoreactivity that is greatest at sulcal depths (asterisks) and is associated with contraction of the cortical ribbon. (D–F) Microscopically, there are dense tau-immunoreactive neurofibrillary tangles (NFTs) and neuropil neurites throughout the cortex, Case A (D), Case B (E), and Case C (F). There are focal nests of NFTs and astrocytic tangles around small blood vessels (E, arrow) and plaquelike clusters of tau-immunoreactive astrocytic processes distributed throughout the cortical layers (F, arrows).

subthalamic nucleus were relatively spared. The lateral substantia nigra pars compacta showed mild neuronal loss, extraneuronal pigment deposition, and moderate numbers of NFTs and NNs. The pars reticulata was unremarkable. The cerebellar peduncle showed mild perivascular hemosiderin deposition. Neurofibrillary tangles were numerous in the dorsal and median raphe nuclei. The internal, external, and extreme capsules, fornix, and mammillothalamic tract showed moderate NNs, although in general, the white matter was less affected than adjacent gray matter.

Case B

There were abundant tau-positive NFTs, glial tangles, and dotlike and spindle-shaped NNs in the superficial layers of cerebral cortex (I-III) (Fig. 3). Cortical tau pathology was most prominent in patchy areas of the superior frontal and temporal lobes, especially the medial temporal lobe, often in a vasocentric pattern. The olfactory bulb, hippocampus, entorhinal cortex, and amygdala showed extremely dense NFTs with many ghost tangles (Figs. 4-6). Tau-positive glia and NNs were also found in the subcortical white matter and corpus callosum. The olfactory bulb, thalamus, hypothalamus, nucleus basalis, striatum, globus pallidus, substantia nigra, raphe, periventricular gray, locus caeruleus, oculomotor nucleus, red nucleus, pontine base, tegmentum, reticular nuclei, inferior olives, and dentate nucleus showed dense NFTs and glial tangles. Spindle-shaped NNs and tau-positive glia were pronounced in the midline white matter tracts of the brainstem.

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Case C

Microscopic examination showed dense accumulations of tau-immunoreactive NFTs, astrocytic tangles, and NNs in irregular patches of the dorsolateral frontal, insular, subcallosal, inferior frontal, superior parietal, and posterior temporo-occipital cortices, and most severely in the medial temporal lobe. The hippocampus, entorhinal cortex, and amygdala contained extremely dense NFTs with ghost tangles and severe neuronal loss (Figs. 4, 6). Tau-positive glia and NNs were also found in the subcortical white matter, particularly in the subcortical U fibers. The olfactory bulb, thalamus, hypothalamus, nucleus basalis, striatum, globus pallidus, substantia nigra, raphe, periventricular gray, locus caeruleus, oculomotor nucleus, red nucleus, pontine base, pontine tegmentum, hypoglossal nuclei, reticular nuclei, inferior olives, midline tracts of the medulla, and dentate nucleus contained dense NFTs and astrocytic tangles (Figs. 5, 7). Subcortical white matter tracts including the anterior and posterior commissure, thalamic fasciculus, and external and extreme capsule also showed astrocytic tangles and NNs.

The abnormal tau proteins that are found in the glial and neuronal tangles in CTE are indistinguishable from NFTs in AD and are composed of all 6 brain tau isoforms (39). Neuropathologically, CTE resembles several other neurodegenerative diseases characterized by accumulations of hyperphosphorylated tau protein in neurons or glial cells, including ALS/PDC of Guam, postencephalitic parkinsonism, PSP, corticobasal degeneration, and frontotemporal

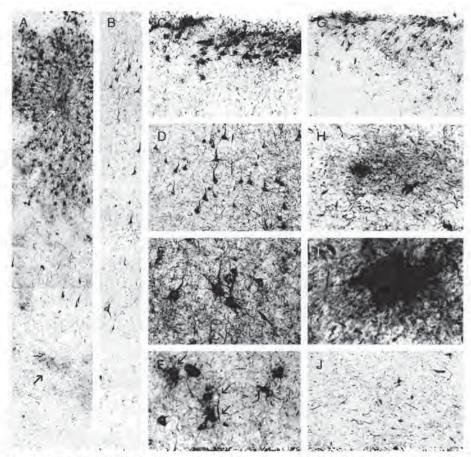


FIGURE 3. Whole-mount 50-μm sections from Cases A and B immunostained with anti-tau monoclonal antibody AT8. (A) Case B. There is a prominent perivascular collection of neurofibrillary tangles (NFTs) and astrocytic tangles evident in the superficial cortical layers with lesser involvement of the deep laminae. Prominent neuropil neurites (NNs) are found in the subcortical U-fibers (arrow). Original magnification: 150×. (B) Case A. There is a preferential distribution of NFTs in Layer II and NNs extending into the subcortical white matter even in mildly affected cortex. Original magnification: 150×. (C) Case A. Focal subpial collections of astrocytic tangles and NFTs are characteristic of chronic traumatic encephalopathy (CTE). Original magnification: 150×. (D) Case A. The shape of most NFTs and NNs in CTE is similar to those found in Alzheimer disease. Original magnification: 150×. Some NFTs have multiple perisomatic processes (E), and spindle-shaped and dotlike neurites are found in addition to threadlike forms. (E) Case A. Original magnification: 350×. (F) Case A. Astrocytic tangles are interspersed with NFTs in the cortex (arrows). Original magnification: 350×. (G) Case A. Tau-immunoreactive astrocytes are common in periventricular regions. Original magnification: 150×. (H, I) Case A. Tau-immunoreactive astrocytes take various forms; some appear to be protoplasmic astrocytes with short rounded processes (H, I) double immunostained section with AT8 (brown) and anti-glial fibrillary acidic protein (red). (H) Original magnification: 350×. (I) Original magnification: 945×. (J) Case B. Dotlike or spindle-shaped neurites predominate in the white matter, although there are also some threadlike forms. Original magnification: 150×.

dementia with parkinsonism linked to chromosome 17 (FTDP-17) (36, 48–50). Similar to ALS/PDC of Guam, neurofibrillary tau pathology in CTE is found in the medial temporal lobe structures, cerebral cortex, and spinal cord, with only a subset of cases showing evidence of diffuse plaques (51). Similar to ALS/PDC and PSP, CTE preferentially involves the superficial cortical layers and involves the accumulation of tau-immunoreactive astrocytes (36). However, CTE differs from ALS/PDC of Guam and PSP in that the cortical involvement is irregular and patchy, greatest at sulcal depths, and distributed in a prominent perivascular, periventricular, and subpial pattern. Furthermore, there is a

unique regional involvement of subcortical and brainstem structures in CTE (Tables 5, 6).

β-Amyloid Deposition

 $\beta\text{-}Amyloid~(A\beta)$ deposition is an inconstant feature in CTE. Fourteen of the 15 brains originally described by Corsellis et al (29) and 6 additional boxers were reexamined by Roberts and colleagues (18) using $A\beta$ immunocytochemistry with formic acid pretreatment; 19 of the 20 cases showed widespread diffuse $A\beta$ deposits. Similarly, Tokuda and colleagues (52) found abundant diffuse $A\beta$ deposits in 8 cases of CTE and cerebrovascular $A\beta$ deposits in 3 cases. In

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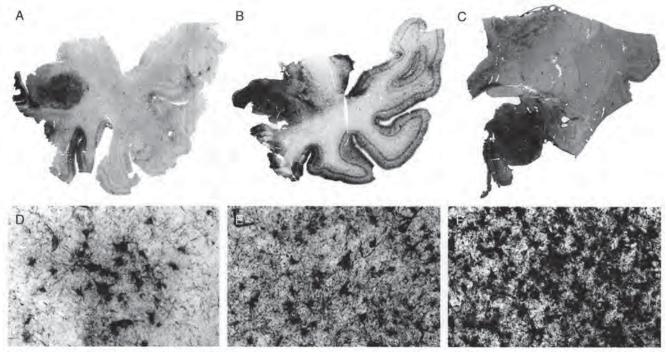


FIGURE 4. (A–C) Whole-mount 50-μm-thick coronal sections immunostained for tau (AT8) from Case A (A), Case B (B), and Case C (C) counterstained with cresyl violet showing extremely dense deposition of tau protein in the amygdala with increasing severity from left to right. (D–F) Microscopically, there is a moderate density of neurofibrillary tangles and astrocytic tangles in Case A (D), the density is increased in Case B (E), and extremely marked in Case C (F). Original magnification: 350×.

our series, only Case B showed moderate numbers of diffuse $A\beta$ plaques in the frontal, parietal, and temporal cortices, and sparse neuritic plaques; there was no vascular amyloid. Of the 51 neuropathologically verified cases of CTE, diffuse plaques were found in 24 (47%), neuritic plaques in 13 (27%), and amyloid angiopathy in 3 (6%). There was also 1 report of a fatal cerebral hemorrhage from amyloid angiopathy associated with CTE (15).

White Matter Changes and Other Abnormalities

Tau-positive fibrillar astrocytic tangles are found in the white matter, but the major abnormality is that of dotlike or

spindle-shaped tau-positive neurites. The shape of the tauimmunoreactive neurites is distinct from the predominantly threadlike forms found in AD and suggests an axonal origin. Tokuda and colleagues (52) characterized the NNs in CTE as shorter and less prominent than the neuropil threads found in AD and not spatially related to senile plaques. Generally, tau abnormalities in the white matter are not as severe as in adjacent gray matter. Other abnormalities frequently found in the cerebral and cerebellar white matter include small arterioles with thickened fibrohyalinized walls with perivascular hemosiderin-laden macrophages, widened perivascular spaces, and white matter rarefaction. In our Cases A to C,

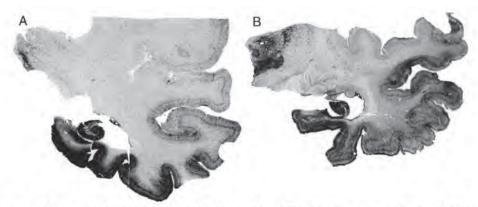


FIGURE 5. Whole-mount 50-μm coronal sections of Case B (A) and Case C (B) immunostained for tau (AT8) and counterstained with cresyl violet. There is extremely dense deposition of tau protein in the hippocampus and medial temporal lobe structures. There is also prominent tau deposition in the medial thalamus.

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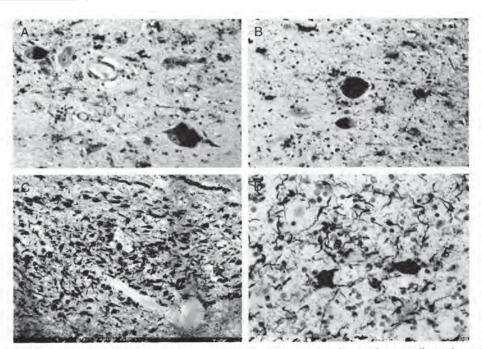


FIGURE 6. Tau-immunoreactive (AT8) neurofibrillary tangles (NFT), astrocytic tangles, and neuropil neurites are found in many subcortical nuclei including the substantia nigra (**[A]** Case C. Original magnification: 350×) and nucleus basalis of Meynert (**[B]** Case C. Original magnification: 350×). The NFTs are also abundant in the olfactory bulb (**[C]** Case B. Bielschowsky silver method. Original magnification: 150×) and thalamus (Case A. Original magnification: 350×. The AT8 immunostain counterstained with cresyl violet).

mild to moderate myelin and axonal losses were found in the corpus callosum and subcortical white matter of the frontal and temporal lobes and cerebellum, with mild perivascular hemosiderin deposition.

α-Synuclein Staining

Extensive accumulation of α -synuclein has been found in axons after acute TBI (53), but α -synuclein immunostaining was not a feature of any of the 51 cases of CTE, including our 3 cases.

CLINICOPATHOLOGIC CONSIDERATIONS

The distribution of the tau abnormalities in CTE suggests distinctive core pathology within the amygdalo-hippocampal-septo-hypothalamic-mesencephalic continuum,

that is, the Papez circuit (54, 55). The early involvement of these anatomical regions, sometimes referred to as *emotional* or *visceral* brain, may underlie many of the early behavioral symptoms, including the tendency toward emotional lability, aggression, and violent outbursts. The early involvement of the hippocampus, entorhinal cortex, and medial thalamus may explain episodic memory disturbance as a frequent presenting symptom (56). Neurofibrillary degeneration of the frontal cortex and underlying white matter most likely contributes to the dysexecutive symptoms. Although less common and generally less severe, neurofibrillary degeneration in the dorsolateral parietal, posterior temporal, and occipital cortices likely accounts for the visuospatial difficulties. The parkinsonian features found in 41.1% of cases are likely caused by degeneration of the substantia nigra pars compacta. The gait

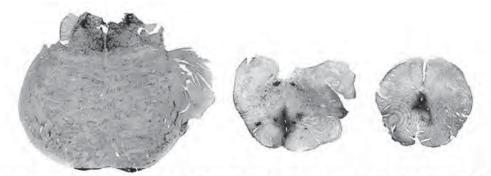


FIGURE 7. Whole-mount tau (AT8)-immunostained 50-µm coronal sections of the brainstem from Case C showing severe involvement of the locus caeruleus, pontine tegmentum, pontine base, midline medulla, and hypoglossal nuclei.

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disorder, variously described as staggered, slowed, shuffled, or frankly ataxic, may result from a combination of cortical and subcortical frontal damage, degeneration of cerebellar tracts in the brainstem, direct cerebellar injury, as well as parkinsonism from substantia nigra pathology. Similarly, speech abnormalities, most often described as slowed and slurred, likely reflect multiregional degeneration. Symptoms of dysarthria, dysphagia, and ocular abnormalities probably result from degeneration of brainstem nuclei, for example, the hypoglossal and oculomotor nuclei.

POSSIBLE MECHANISMS OF CEREBRAL INJURY

Acceleration and deceleration forces are thought to be important events in concussion, particularly rotational acceleration and deceleration (57–59). Sagittal (front-to-back) injuries result in relatively good recovery, whereas lateral (side-to-side) injuries produce the most injury, with injury directed related to the severity of the generating force (58). Conceivably, a concussive impact imparts a fluid wave in the lateral ventricles that produces a shearing force on the septum pellucidum; this may explain the development of an enlarged cavum septum pellucidum and, if severe or repeated, fenestrations.

The patchy irregular location of the cortical NFTs and astrocytic tangles suggests that the distribution is related to direct mechanical injury from blows to the side or top of the head, given their multifocal dorsolateral frontal and parietal, inferior frontal and occipital, and lateral temporal distribution. The possibility that ischemia may contribute to the development of the tau pathology is suggested by the concentration of tau-immunoreactive pathology at the depths of sulci. Damage to the blood-brain barrier and release of local neurotoxins might explain some of the tendency toward perivascular nests of tau-immunoreactive NFT, tau-positive glia, and NNs (13). Buee et al (60) studied the microvasculature of several cases of dementia pugilistica and found decreased microvascular density and tortuosity, with a strong correlation between the laminar distribution of NFTs and pathological microvasculature. Buee and colleagues (60) suggested that the shear forces of repetitive head trauma might lead to vascular damage followed by perivascular NFT and NN formation. Further supporting a possible vascular connection to the pathological changes in CTE, Bouras et al (61) reported that, upon laser microprobe mass analysis, NFTs and nuclei of NFT-free neurons in CTE contained substantially higher amounts of iron and aluminum than NFTs in AD.

Acute TBI

Axonal Injury

Acute concussion produces diffuse axonal injury (62). The "diffuse degeneration of the cerebral white matter" was first described by Strich (63) as the shearing or mechanical tearing of axons at the time of injury. It is now appreciated that axons are not sheared at the time of injury, except in the most severe instances of diffuse axonal injury, but instead undergo a series of changes that may result in a secondary axotomy within 24 hours (64). The axolemma is one of the initial sites of injury; the increased permeability, uncontrolled

influx of Ca++, swelling of mitochondria, disruption of microtubules, and alterations in axonal transport that follow produce axonal swelling and secondary axotomy (64-66). Rapid axonal swelling, perisomatic axotomy, and Wallerian degeneration may also occur without changes in axolemmal permeability, suggesting that trauma may have diverse effects on axons. McKenzie et al (67) showed that 80% of patients who died of acute head injury showed immunocytochemical evidence of axonal injury within 2 hours of injury; after 3 hours of injury, axonal bulbs were identified, and as the survival time increased, the amount of axonal damage and axonal bulb formation increased. Axonal injury was found most frequently in the brainstem, followed by the internal capsule, thalamus, corpus callosum, and parasagittal white matter (67). Axonal damage may continue for weeks after the acute TBI (68).

Deposition of Abnormal Proteins

In individuals undergoing surgical brain tissue resection for acute TBI, tau-immunoreactive dystrophic axons were found in the white matter, and diffuse tau immunoreactivity was found in some neuronal cell bodies, dendrites, and glial cells within 2 to 3 hours postinjury (67). Studies of acute TBI in experimental animal models and postmortem human brain also demonstrate that AB deposition and amyloid precursor protein processing, production, and accumulation are increased after injury (69-78). Increased amyloid precursor protein production in experimental TBI has also been associated with heightened neuronal loss in the hippocampus (73, 79). In acute TBI, diffuse cortical AB plaques have been found in 30% to 38% of cases as early as 2 hours after injury (73, 76, 80). In addition, individuals with cortical A β plaques showed increased levels of soluble A β_{42} , and half were apolipoprotein E (ApoE) &4 allele carriers (81). In acute TBI, AB deposition is widely distributed throughout the neocortex without apparent association with the injury sites (82). The predominant form of A β in acute TBI is A β_{42} , whereas the AB40 form predominates in serum and cerebrospinal fluid, a situation similar to that in AD (83). A recent report also showed that interstitial soluble Aβ concentrations in the brain seem to directly correlate with neurological outcome after TBI (84).

NEURONAL DEATH IN ACUTE TBI AND RELATIONSHIP TO CTE

There are multiple reasons for neuronal loss in acute traumatic injury including neuronal death from direct physical damage, necrosis from the immediate release of excitatory transmitters such as glutamate, and diffuse delayed cell death involving both necrotic and apoptotic death cascades (85, 86). Other contributing factors include focal ischemia, breakdown of the blood-brain barrier, inflammation, and the release of cytokines. Experimental lateral percussive injury in the rat produces apoptotic and necrotic neuronal death that progresses for up to 1 year after injury, with degeneration of the cortex, hippocampi, thalami, and septum, ventriculomegaly, and impaired memory performance (62, 85, 87–89). The thalamic degeneration typically follows the cortical degeneration by weeks, suggesting that a secondary process

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such as deafferentation may play a role in the thalamic neuronal death. Neuronal loss in the hippocampus and thalamus has also been reported after blunt head injury in humans using stereological techniques (90, 91). One of the key features of CTE is that the disease continues to progress decades after the activity that produced traumatic injury has stopped. It is most likely that multiple pathological cascades continue to exert their effects throughout the individual's lifetime once they are triggered by repetitive trauma; the longer the survival after the initial events and the more severe the original injuries, the greater the severity of the neurodegeneration. It is clear that neuronal loss, cerebral atrophy, and ventricular enlargement all increase with longer survival and greater exposure to repetitive trauma.

DIAGNOSIS OF CTE

Presently, there are no available biomarkers for the diagnosis of CTE. Although significant decreases in cerebrospinal fluid ApoE and AB concentrations have been reported that correlated with severity of the injury after TBI, there have been no similar studies in CTE (92). Nonetheless, advances in neuroimaging offer the promise of detecting subtle changes in axonal integrity in acute TBI and CTE. Standard T1- or T2-weighted structural MRI is helpful for quantitating pathology in acute TBI, but diffusion tensor MRI (DTI) is a more sensitive method to assess axonal integrity in vivo (93, 94). In chronic moderate-to-severe TBI, abnormalities on DTI have been reported in the absence of observable lesions on standard structural MRI (83). More severe white matter abnormalities on DTI have been associated with greater cognitive deficits by neuropsychological testing (94, 95), and increases in whole-brain apparent diffusion coefficient and decreases in fractional anisotropy using DTI have been found in boxers compared with controls (96, 97).

GENETIC RISK AND THE ROLE OF APOE4

Apolipoprotein E genotyping has been reported in 10 cases of CTE, including our most recent cases. Five (50%) of the 10 cases of CTE carried at least 1 ApoE ϵ 4 allele, and 1 was homozygous for ApoE ϵ 4 (our Case A). The percentage of ApoE ϵ 4 carriers in the general population is 15%; this suggests that the inheritance of an ApoE ϵ 4 allele might be a risk factor for the development of CTE.

In acute TBI, there is accumulating evidence that the deleterious effects of head trauma are more severe in ApoE ϵ 4–positive individuals (98–100). Acute TBI induces A β deposition in 30% of people (75, 76), and a significant proportion of these individuals are heterozygous for ApoE ϵ 4 (101, 102). Apolipoprotein E4 transgenic mice experience greater mortality from TBI than ApoE ϵ 3 mice (102). Furthermore, transgenic mice that express ApoE ϵ 4 and overexpress amyloid precursor protein show greater A β deposition after experimental TBI (103).

GUIDELINES FOR PREVENTION AND TREATMENT

Clearly, the easiest way to decrease the incidence of CTE is to decrease the number of concussions or mild TBIs.

In athletes, this is accomplished by limiting exposure to trauma, for example, by penalizing intentional hits to the head (as is happening in football and hockey) and adhering to strict "return to play" guidelines. Proper care and management of mild TBI in general and particularly in sports will also reduce CTE. No reliable or specific measures of neurological dysfunction after concussion currently exist, and most recommendations are centered on the resolution of acute symptoms such as headache, confusion, sensitivity to light, and so on (104). Asymptomatic individuals have been shown, however, to have persistent decreases in P300 amplitudes in response to an auditory stimulus at least 5 weeks after a concussion, thereby casting doubt on the validity of the absence of symptoms as a guidepost (105, 106). Neuropsychological tests have also helped provide estimates of the appropriate time for athletes to return to practice and play. Studies using event-related potentials, transcranial magnetic stimulation, balance testing, multitask effects on gait stability, positron emission tomography, and DTI MRI have all shown abnormalities in concussed athletes or nonathletes with TBI lasting for 2 to 4 weeks (105, 107-109). These studies indicate that safe return to play guidelines might require at least 4 to 6 weeks to facilitate more complete recovery and to protect from reinjury, as a second concussion occurs much more frequently in the immediate period after a concussion (106, 110). In addition, experimental evidence in animals suggests that there is expansion of brain injury and inhibition of functional recovery if the animal is subjected to overactivity within the first week (111).

CONCLUSIONS

Chronic traumatic encephalopathy is a progressive neurodegeneration clinically associated with memory disturbances, behavioral and personality changes, parkinsonism, and speech and gait abnormalities. Pathologically, CTE is characterized by cerebral and medial temporal lobe atrophy, ventriculomegaly, enlarged cavum septum pellucidum, and extensive tau-immunoreactive pathology throughout the neocortex, medial temporal lobe, diencephalon, brainstem, and spinal cord. There is overwhelming evidence that the condition is the result of repeated sublethal brain trauma that often occurs well before the development of clinical manifestations. Repetitive closed head injury occurs in a wide variety of contact sports as well as a result of accidents or in the setting of military service. Pathologically, CTE shares some features of AD, notably tau-immunoreactive NFTs, NNs, and in approximately 40% of cases, diffuse senile plaques. Furthermore, the AB and NFTs found in CTE are immunocytochemically identical to those found in AD, suggesting a possible common pathogenesis. Multiple epidemiological studies have shown that head injury is a risk factor for AD, and there have been several case reports citing an association between a single head injury and the development of subsequent AD (112, 113). Just as acquired vascular injury may interact additively or synergistically with AD, traumatic injury may interact additively with AD to produce a mixed pathology with greater clinical impact or synergistically by promoting pathological cascades that result in either AD or CTE. In athletes, by instituting and following proper

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guidelines for return to play after a concussion or mild TBI, it is possible that the frequency of sports-related CTE could be dramatically reduced or, perhaps, entirely prevented.

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APPENDIX

Methods for Analysis of Cases A to C

The following anatomical regions were microscopically evaluated in paraffin sections in Cases A to C: olfactory bulb, midbrain at level of red nucleus, right motor cortex, right inferior parietal cortex (Brodmann Area [BA] 39, 40), right anterior cingulate (BA 24), right superior frontal (BA 8, 9), left inferior frontal cortex (BA 10, 11, 12), left lateral frontal (BA 45, 46), caudate, putamen, and accumbens (CAP), anterior temporal (BA 38), superior temporal (BA 20, 21, 22), middle temporal cortex, inferior temporal cortex, amygdala, entorhinal cortex (BA 28), globus pallidus, insula, substantia innominata, right hippocampal formation at the level of the lateral geniculate, hippocampus, thalamus with mammillary body, thalamus, posterior cingulate (BA 23, 31), calcarine cortex (BA 17,18), superior parietal cortex (BA 7B), cerebellar vermis, cerebellum with dentate nucleus, parastriate cortex (BA 19) pons, medulla, and spinal cord.

The sections were stained with Luxol fast blue and hematoxylin and eosin, Bielschowsky silver impregnation, and by immunohistochemistry with antibodies to phosphoserine 202 and phosphothreonine 205 of PHF-tau (mouse monoclonal AT8; Pierce Endogen, Rockford IL; 1:2000), α-synuclein (rabbit polyclonal; Chemicon, Temecula, CA; 1:15,000), AB (mouse monoclonal; Dako North America Inc, Carpinteria, CA; 1:2000) (after formic acid pretreatment), and Aβ 42 (rabbit polyclonal; Invitrogen [Biosource], Carpinteria, CA; 1:2000). In addition, multiple large coronal fragments were cut at 50 µm on a sledge microtome and stained as free-floating sections using a mouse monoclonal antibody directed against phosphoserine 202 of tau (CP-13; courtesy of Peter Davies; 1:200); this is considered to be the initial site of tau phosphorylation in NFT formation (114-118). Other monoclonal antibodies used for immunostaining were AT8, phosphoserine 396, and phosphoserine 404 of hyperphosphorylated tau (PHF-1; courtesy of Peter Davies; 1:1000) (114-118), glial fibrillary acidic protein (Chemicon; 1:2000), and HLA-DR-Class II major histocompatibility complex (LN3; Zymed, San Francisco, CA; 1:2000); some of these sections were counterstained with cresyl violet.

EXHIBIT 54

CHRONIC TRAUMATIC ENCEPHALOPATHY IN THE NATIONAL FOOTBALL LEAGUE

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hen Andre Waters, a hard hitting National Football League (NFL) safety from 1984 to 1995, made the front page of the New York Times on Thursday, January 18, 2007, he became the third NFL player known to have died as a result of chronic traumatic encephalopathy (CTE) attributed to the multiple concussions he experienced while playing in the NFL. Preceding the 44-year-old Andre were Mike Webster, age 50, the Hall of Fame Pittsburgh Steelers center who died homeless, and Terry Long, age 42, who, like Waters, took his own life (6, 7).

All three of these athletes were known as iron men, hard hitters who never came out of the game, continuing to play through countless injuries, including concussions. All of these athletes, as well as Ted Johnson, whose frontpage story was widely circulated February 2, 2007 in the New York Times and Boston Globe, shared symptoms of sharply deteriorated cognitive function, especially recent memory loss and psychiatric symptoms such as paranoia, panic attacks, and major depression after multiple concussions experienced in the NFL.

The brains of all of these deceased athletes were examined by Bennett Omalu, M.D., a forensic pathologist at the University of Pittsburgh, and shared common features of CTE including neurofibrillary tangles, neutrophil threads, and cell dropout. He likened Waters' brain to that of an "octogenarian Alzheimer's patient."

ARE THE FINDINGS OF CTE IN THE BRAINS OF WEBSTER, LONG, AND WATERS A SURPRISE?

Certainly the Waters finding was no surprise to Julian Bailes, M.D., medical director, and Kevin Guskiewicz, Ph.D., the Director of the Study of Retired Athletes at the University of North Carolina at Chapel Hill. Their study of retired NFL players published in this journal found that those who had sustained three or more concussions were three times more likely to experience "significant memory problems" and five times more likely to develop earlier onset of Alzheimer's disease (3). A study published this year by the same authors found a similar relationship between three or more concussions and clinical depression (4).

The NFL's own publications in this journal on concussion state that they had seen no cases of CTE in the NFL (8-10). That finding is not a surprise as the NFL study included only active players in their 20s and 30s during a short 6-year window from 1996 to 2001. Other significant limitations of the NFL studies include the following:

- 1) History of concussion: previous concussions either in the NFL in the years before the study began or during their playing careers in high school, college, or other levels of football were not included.
- 2) The population of NFL players changes from year to year: new players enter the league, older players leave the league, and we do not know the number of players who constituted the 1996 population who are still in the league in subsequent years.
- 3) There was difficulty collecting data on loss of consciousness; the initial data collection sheet did not ask for data regarding loss of consciousness.
- 4) This was a multisite study with numerous different examiners; there was no uniform method of evaluation of concussion in this study.
- 5) Return to play data were collected on players with initial and repeat concussion: there are many other factors that go into the decision of whether or not the player should return to play, including the importance of the player to the team; the importance of the upcoming game to the team; and pressure from owners, players, and their families, coaches, agents, and media may certainly influence the final decision on when the player returns to play.

6) The results apply to mainly NFL-level players: extrapolation to younger players has not been demonstrated.

Should we be surprised that CTE has been reported in former NFL football players? I would echo Dr. Bailes and say "absolutely not," but for additional reasons. Before I enumerate, let us first go back to the definition of CTE.

CTE, or dementia pugilistica, was first described by Harrison S. Martland in his landmark *Journal of the American Medical Association* article published in 1928 (5) as being characteristic of boxers "who take considerable head punishment seeking only to land a knockout blow." It was also "common in second rate fighters used for training purposes." The early symptoms he described were a "slight mental confusion, a general slowing in muscular movement, hesitancy in speech, and tremors of the hands." Later, marked truncal ataxia, Parkinsonian syndrome, and marked mental deterioration may set in, "necessitating commitment to an asylum" (5, p 1103).

Although Martland first described the clinical syndrome of CTE and Roberts (11) echoed the dangers of chronic brain damages in boxers in 1969, it was Corsellis et al. who first identified the neuropathology of this syndrome in the brains of 15 deceased boxers, eight of whom were either world or national champions (1).

Table 1 summarizes his findings of the four main components of this entity, areas of the brain damaged, and resultant signs and symptoms. It is critical to understand that although Corsellis pointed out four different areas of the brain and the resultant signs and symptoms, he did not state that all four areas needed to be involved for the diagnosis to be made. In fact, only eight out of 15 brains studied had all four areas of pathology present (2).

It was Corsellis who also reported CTE not only in boxers but other sports with a high risk of head injury, including those in which head injury occurred in declining frequency; among these were jockeys (especially steeplechasers), professional wrestlers, parachutists, and even a case of battered wife syndrome. With this history, it is no surprise to have cases from NFL football.

TABLE 1. Four main components of chronic brain damage in dementia pugilistica

dementia pugnistica	
Area damaged	Clinical symptoms/signs
Septum pellucidum, adjacent periventricular grey matter, frontal and temporal lobes	Altered affect (euphoria, emotional ability) and memory
Degeneration of the substantia nigra	Parkinson's syndrome of tremor, rigidity, and brachykinesia
Cerebellar scarring and nerve cell loss	Slurred speech, loss of balance and coordination
Diffuse neuronal loss	Loss of intellect, Alzheimer's syndrome

SO WHAT ARE THE QUESTIONS TO BE ANSWERED?

The most pressing question to be answered concerns the prevalence of the problem. The Waters case came to light only because of Chris Nowinski, a former All-Ivy defensive tackle at Harvard and World Wrestling Entertainment professional wrestler who, after being forced to retire because of repeated concussions and postconcussion syndrome, researched and wrote a book on the subject of athletic concussions. Hearing of Waters' suicide and suspecting CTE, Nowinski convinced the Waters family to send a portion of Waters' brain to Dr. Omalu for neuropathological examination.

Since the Ted Johnson publicity in which this former New England Patriots star middle linebacker said, "I don't want anyone to end up like me," I have personally examined and spoken with a number of retired NFL players with postconcussion/CTE symptoms. Only an immediate prospective study will determine the true incidence of this problem. Although this study could be funded by the NFL charities, the NFL should refrain from introducing potential bias with regard to the team of neurosurgeons, neurologists, neuropsychiatrists, and neuropathologists with athletic head injury expertise chosen to carry out the study.

I also commend the fact that the brains of Webster, Long, and Waters have now been examined by other neuropathologists who concur with Omalu's findings. Obtaining second opinions on such a high profile issue is just common sense.

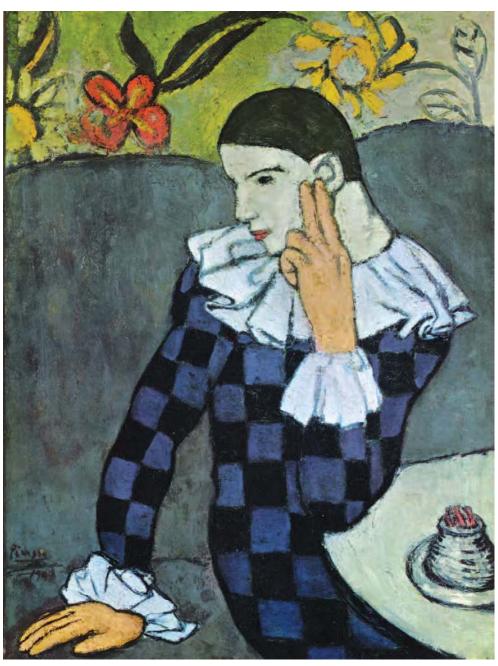
Finally, it is clear that not all players with long concussion histories have met premature and horrific ends to their lives. However, as the list of NFL players retired as a result of postconcussion symptoms (e.g., Harry Carson, Al Toon, Merrill Hodge, Troy Aikman, Steve Young, Ted Johnson, Wayne Chrebet) grows and as the number of documented CTE cases increases, I believe the time for independent study of the problem as well as NFL recognition that there is a problem is now. Recognizing that soldiers were having problems with blastrelated closed head injury, I have been a part of a team convened by the Department of Defense to write management algorithms and protocols in the past year. I believe the NFL would be prudent to assemble such an independent impeccably qualified "dream team" to tackle their problem with concussion and resultant CTE head on. Just as the National Association for Stock Car Auto Racing recently faced a problem, solved it, and became even more popular, I believe the NFL will lift this dark cloud if they confront the problem directly and honestly.

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Harlequin by Picasso, 1901. Oil on canvas. Courtesy of The Metropolitan Museum of Art, New York.

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CLINICAL STUDIES

ASSOCIATION BETWEEN RECURRENT CONCUSSION AND LATE-LIFE COGNITIVE IMPAIRMENT IN RETIRED PROFESSIONAL FOOTBALL PLAYERS

OBJECTIVE: Cerebral concussion is common in collision sports such as football, yet the chronic neurological effects of recurrent concussion are not well understood. The purpose of our study was to investigate the association between previous head injury and the likelihood of developing mild cognitive impairment (MCI) and Alzheimer's disease in a unique group of retired professional football players with previous head injury exposure.

METHODS: A general health questionnaire was completed by 2552 retired professional football players with an average age of 53.8 (±13.4) years and an average professional football playing career of 6.6 (± 3.6) years. A second questionnaire focusing on memory and issues related to MCI was then completed by a subset of 758 retired professional football players (≥50 yr of age). Results on MCI were then cross-tabulated with results from the original health questionnaire for this subset of older retirees.

RESULTS: Of the former players, 61% sustained at least one concussion during their professional football career, and 24% sustained three or more concussions. Statistical analysis of the data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, df = 2, P = 0.02) and self-reported significant memory impairments ($\chi^2 = 19.75$, df = 2, P = 0.001). Retired players with three or more reported concussions had a fivefold prevalence of MCI diagnosis and a threefold prevalence of reported significant memory problems compared with retirees without a history of concussion. Although there was not an association between recurrent concussion and Alzheimer's disease, we observed an earlier onset of Alzheimer's disease in the retirees than in the general American male population

CONCLUSION: Our findings suggest that the onset of dementia-related syndromes may be initiated by repetitive cerebral concussions in professional football players.

KEY WORDS: Alzheimer, Concussion, Mild cognitive impairment, Retired professional football players

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raumatic brain injury (TBI) is an important public health concern, as each year more than 1.2 million Americans suffer head injury (26). More than 50,000 headrelated injuries result in a fatality each year in the United States, whereas the overwhelming majority of head injuries are classified as mild traumatic brain injuries that can result in significant cognitive, emotional, and functional disabilities (26). TBI has been identified as a potential risk factor for the occurrence (or early expression) of neurodegenerative dementing disorders, including Alzheimer's dis-

ease (AD) disease and Parkinson's syndrome, and other psychiatric disorders such as clinical depression (8, 13, 21, 25, 28, 31, 35–37, 40). Still, other research findings have not shown this association between TBI and dementia (1, 3, 6, 7, 17, 19, 33, 42). Guo et al. (9) suggested that the severity of head injury is related to the magnitude of AD risk, and that the risk of AD associated with head injury involving loss of consciousness was approximately double that associated with head injury without loss of consciousness. However, they reported that even head injury without loss of conscious-

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ness significantly increased the risk of AD relative to no head injury (9).

Mild cognitive impairment (MCI) is a recently established diagnostic classification typically applied to older individuals who exhibit some evidence of cognitive decline (usually in the domain of memory) and perform below expected levels on formal neurocognitive testing, but who have not exhibited a sufficient degree of impairment and/or functional decline to meet diagnostic criteria for dementia (30). MCI is often conceptualized as a transitional state between the cognitive changes of normal aging and dementia, with most recent studies estimating that 10 to 20% of MCI patients convert to a more advanced stage labeled as "dementia" each year, compared with healthy controls who convert at a rate of 1 to 2% per year (5, 22, 39). The majority of patients with MCI who convert to dementia are subsequently diagnosed with probable AD, although a significant percentage is diagnosed with vascular dementia (23). The identification of risk factors for the onset of MCI, and for the conversion of MCI to dementia, is an important step in developing strategies for the prevention and early treatment of these disorders, especially with the emergence of various dementia treatment agents thought to provide the greatest therapeutic yield earliest in the disease process. Although head trauma has been linked to irreversible cognitive deficits (24, 29, 30), its role in causing eventual MCI or AD is less clear. Mayeux et al. (20) reported a 10-fold increase in the risk of developing AD among those individuals who tested positive for the ApoE e4 gene and had a history of TBI, compared with only a two-fold increase in risk with the ApoE e4 gene alone. Other authors have described a genetic vulnerability and redistribution of neurofilaments after TBI resulting from rotational acceleration of the head in the nonathletic population (12, 27).

The relatively high rate of concussive brain injuries in contact sports affords a unique opportunity for exploring both the immediate and long-term consequences of concussion. More than 300,000 sport-related concussions, many of which are recurrent injuries, occur annually in the United States (38). Unfortunately, the long-term effects of these concussions remain largely unclear. Organized sports, however, provides for a unique laboratory for studying the influence of recurrent mild TBI on dementia-related syndromes such as MCI and AD. The sports literature has connected ApoE e4 with chronic TBI in boxers (16), and other studies have shown that the repeated head trauma experienced by boxers can lead to the development of dementia pugilistica-punch drunk syndrome (32). This literature has also carefully defined the neuropathology of dementia pugilistica as involving numerous neurofibrillary tangles in the absence of plaques, in contrast to the profusion of tangles and plaques seen in AD. Lower cognitive performance has also been found in older football players with the ApoE e4 gene, suggesting that there may be an association between these dementia syndromes and either recurrent TBI or recurrent subconcussive contacts to the head (18). The purpose of our study was to investigate the association between previous head injury and the likelihood of

developing MCI and/or AD in a unique group of individuals, namely retired professional football players, who have previous head injury exposure.

PATIENTS AND METHODS

A diverse group of retired professional football players were studied, including recent retirees and those who played professional football before World War II. All participants played a minimum of two seasons of professional football. We studied this group using two self-report questionnaires: a general health survey and a follow-up instrument specifically targeting cognitive decline. It was explained at the beginning of the survey that participants would not be identified and that research records would be kept confidential. By completing and submitting the survey, participants were acknowledging that they agreed to take part in this research study.

General Health Questionnaire

The general health questionnaire was first sent to all living members of the National Football League Retired Player's Association (n = 3683) through the Center for the Study of Retired Athletes. The questionnaire asked a variety of questions about musculoskeletal, cardiovascular, and neurological conditions that the retired player experienced during and after his football career. It included questions about the number of concussions sustained during their professional football career (concussion history) and the prevalence of diagnosed medical conditions such as depression, Parkinson's disease, AD, and schizophrenia. Previous concussion was based on the player's retrospective recall of injury events and was defined on the questionnaire as an injury resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and difficulty concentrating. Additionally, the questionnaire included the SF-36 Measurement Model for Functional Assessment of Health and Well-Being, which addresses how well the retired athlete functions with activities of daily living (41). From the SF-36, we calculated a physical health composite score, which includes scores of physical functioning, role physical, bodily pain, and general health, as well as a mental health component score, which includes scores of vitality, social functioning, role emotional, and mental health. These scores were compared with age- and genderspecific population-based norms established by previous researchers (41).

We initially mailed the general health questionnaire in May 2001, followed by remailings to nonrespondents in August 2001 and February 2002. We then began telephoning nonrespondents at different times of the day and completed the questionnaire over the telephone. We then conducted a reliability check of the general health questionnaire by readministering the instrument to 25 of the original respondents 18 to

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24 months later to establish a high level of agreement between selected responses.

Mild Cognitive Impairment Instrument

Approximately 4 months later, a second questionnaire focusing on memory and issues related to MCI was sent to a subset of 1754 retirees. The subset comprised all respondents from the original health questionnaire who were aged 50 years or older. The same instrument was also sent to an informant (spouse or close relative) to collect data on any cognitive problems exhibited by the retiree that were not reported on the retiree's instrument. Results from the MCI questionnaire were then cross-tabulated with results from the original general health questionnaire. MCI was defined according to the following, outlined in the American Academy of Neurology Practice Parameter (30): memory complaint corroborated by a family member; objective memory impairment as determined by neurocognitive testing; intact activities of daily living; and does not meet accepted diagnostic criteria for probable AD or other forms of dementia.

Statistical Analysis

X² tests of association were used to compare proportions in tables; Fisher's exact test was used when 80% of expected cell counts were less than five. Analysis of variance models were used to determine differences among the groups on selected variables. The groups were stratified by concussion history (none, one, two, and three or more). Because of the sample size, some analyses required us to collapse respondents with one and two previous concussions into a single group (one to two previous concussions). We used the Cochran-Armitage trend test to assess linear trends in the proportion of retirees reporting memory impairments and problems across strata of concussion history. Level of significance for all analyses was set a priori at P < 0.05. Estimates of the prevalence of AD in the general population of American men, stratified by age, were provided by researchers at the Johns Hopkins University (2).

RESULTS

General Health Questionnaire

Of the original 3683 general health surveys sent to retired players, 2552 (69.3%) were completed. The age of the respondents averaged 53.8 (± 13.4) years, with an average professional football playing career of 6.6 (± 3.6) years. Respondents reported having played organized football (junior high school, high school, college, armed service, and professional) for an average of 15.1 (± 4.3) years. When considering the prevalence of previous concussions, 1513 (60.8%) of the retired players reported having sustained at least one concussion during their professional playing career, and 597 (24%) reported sustaining three or more concussions. Of those retired players who had sustained a concussion during their professional career, more than half reported experiencing loss of consciousness (n = 817,

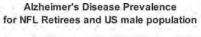
54.0%) or memory loss (n = 787, 52.0%) from at least one of their concussive episodes. We asked the retired athletes for their subjective assessment of the long-term consequences of their injuries. Of the retirees who sustained at least one concussion, 266 (17.6%) reported that they perceived the injury to have had a permanent effect on their thinking and memory skills as they have gotten older.

Only 33 (1.3%) retired players reported being diagnosed by a physician as having AD; 15 were undergoing medical treatment for the disease. We observed a higher prevalence of AD in the study population relative to the general American male population (Fig. 1). The overall age-adjusted prevalence ratio for AD was 1.37 (95% confidence interval 0.98-1.56), which indicates that the football retirees have higher prevalence than other American men of the same age. The AD prevalence in the football retirees was particularly increased in the younger age groups (≤70 yr), which suggests that this group may have an earlier onset of AD than the general American male population. The average age of the retired players with AD was 71.7 (\pm 7.62) years (range, 52–83 yr). There was, however, no association between number of concussions sustained as a professional player (none, one, two, and three or more) and a diagnosis of AD (Fisher's exact test, P = 0.24).

Mental Component Scale (MCS) scores on the SF-36 were similar between the NFL retirees and population-based normative values for all age groups (P > 0.05) (Fig. 2); however, retired players with a history of concussion, especially recurrent concussion, scored lower (worse) on the MCS than those without a history of recurrent concussion (F [3,2146] = 19.29, P = 0.001). The lowest MCS scores were observed in those with the most reported concussions (Table 1). The group who experienced three or more concussions also scored significantly worse than the normative group on the age-matched MCS (50.31 versus 52.42).

Mild Cognitive Impairment Instrument

Results of the follow-up MCI and memory questionnaires were analyzed based on responses from 758 retired players (average age, 62.4 yr) and 641 retired players' spouses or close relatives. Our findings revealed 22 cases of physician-diagnosed MCI and 77 cases of retirees who have significant



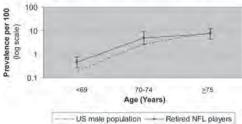


FIGURE 1. Alzheimer's disease prevalence ratios for the American male population and National Football League (NFL) retirees. Error bars indicate 95% confidence intervals.

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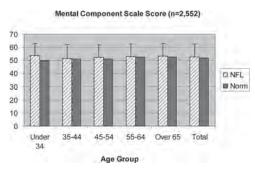


FIGURE 2. MCS scores for the NFL retirees and population norms by age. "Total" is age-standardized; error bars indicate 95% confidence intervals.

TABLE 1. Mental Component Scale score by concussion history in retired National Football League players aged 50 years or older^a

No. of previous concussions	Mean MCS score and 95% CI	Standard deviation
0 (n = 814)	54.35 (53.77, 54.94)	(8.50)
1 (n = 429)	52.63 (51.73, 53.52)	(9.47)
2 (n = 374)	52.97 (52.03, 53.91)	(9.22)
3 + (n = 533)	50.31 (49.35, 51.27)	(11.26)

 $[^]a$ MCS, mental component scale; CI, confidence interval. P< 0.001; β -1 51 (0.26)

memory impairment as determined by their spouse or close relative. Further analyses of these data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, df = 2, P = 0.02); self-reported significant memory impairments ($\chi^2 = 19.75$, df = 2, P = 0.001); and spouse/relative-reported significant memory impairments (χ^2 = 6.05, df = 2, P = 0.04). Retired players with three or more reported concussions had a fivefold prevalence of being diagnosed with MCI and a threefold prevalence of reported significant memory problems compared with those players without a history of concussion (Fig. 3). There was no association between MCI and other systemic factors such as coronary heart disease, hypertension, diabetes, or osteoarthritis. Although we found an association between diagnosis of MCI and stroke, this association does not detract from the association between MCI and concussion history. Only three (13.6%) of the 22 MCI cases involved stroke, and we do not know which diagnosis came first.

DISCUSSION

These data suggest that a history of concussion, particularly recurrent concussion, may be a risk factor for the expression of late-life memory impairment, MCI, and AD. Although the

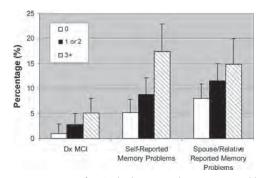


FIGURE 3. Percentage of retired players aged 50 years or older with a diagnosis of MCI and memory problems (self-reported and reported by a spouse or close relative) by concussion history (none, one, two, and three or more). Error bars indicate 95% confidence intervals. P < 0.007.

clinical samples studied are relatively small, retired professional football players were found to have a progressive decline in mental health functioning and a higher rate of memory problems and cognitive decline associated with a history of concussion. Retired players with a history of three or more concussions were at highest risk of being diagnosed by a physician as having MCI and of having significant memory problems based on their own account and the observations of their spouse or caregiver.

Data from a small sample of retired athletes medically diagnosed with probable AD also suggests a trend toward earlier disease onset and higher disease prevalence in younger cohorts relative to the general population (Fig. 1). Despite the earlier onset of AD, we failed to find an association between previous concussion and lifetime onset of AD. The cumulative effect of sub-concussive and concussive contacts to the head sustained by professional football players may promote an earlier expression of AD; however, the factor of age eventually overwhelms this factor and prevents it from becoming an independent predictor of lifetime onset of AD. Thus, the lines in Figure 1 representing the two groups (American male population and retired NFL players) eventually converge.

The number of individuals in the United States with AD was estimated at 2.32 million in 1997, and it is projected that the prevalence will nearly quadruple in the next 50 years, by which time 1 in 45 Americans will be afflicted with the disease (2). As a result, AD is sure to place a large burden on the country's health care system in the decades ahead. For this reason, identification of factors associated with precursor conditions to AD are of interest. The pathology is characterized by cerebral atrophy most severe in frontal, temporal, and parietal lobes resulting in a dramatic reduction of brain weight (normal, 1500-1800 g; AD, 850-1250 g). Microscopic findings include senile plaques, neurofibrillary tangles, and granulovascular degeneration. Biomechanically, there is a 50 to 90% reduction in choline acetyltransferase (5, 15, 17, 23, 36, 37, 39). Clinically, AD presents with a progressive decline in cortical functions principally affecting memory, language, and executive functioning, followed by increasing neurobehavioral and

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neuropsychiatric deficits in more advanced stages of the disease (2, 5, 6).

The study of MCI and AD is challenging because of the difficulties in diagnosing the conditions. Both conditions can be evaluated using several measures, but they cannot be diagnosed solely on neuropsychological assessment. Petersen et al. (29, 30) state that the usefulness of any neuropsychological battery for identifying cases of MCI depends on its composition, size, and supporting data. The battery should include measures of new learning, delayed recall, attention, and executive function. Neuroimaging is also considered a powerful tool for the differential diagnosis of cognitive impairment and tracking change (30). Hippocampal atrophy has been identified in amnestic MCI relative to cognitively intact controls, and it is believed that volumetric measurement of this atrophy can predict the rate of conversion from MCI to AD (15).

The human ApoE gene encodes a cholesterol carrier lipoprotein (apolipoprotein E) that is made in the liver and brain and is important in the transport of lipids in the brain. There are three allelic forms (ApoE e2, e3, e4) that give rise to six possible genotype combinations. ApoE plays an important role in the response of the brain to injury. After accelerator forces are imparted to the brain, there is an accumulation of beta amyloid and tau proteins within hours of injury within the neuronal body (12). Possession of the e2 allele is now believed to be underrepresented in AD and may be protective (22). On the other hand, possession of ApoE e4 increases the risk of AD, shifts onset to an earlier age, increases the accumulation of amyloid beta protein in AD and TBI, and decreases recovery after TBI (6, 7, 12, 19, 20).

The sports literature also suggests that possessing the ApoE e4 allele results in greater cognitive impairment after mild repetitive head injury. Older professional football players with the ApoE e4 allele score lower on cognitive tests than players without the allele or less experienced players of any genotype (18). The study clearly suggests that the cognitive status of athletes with repeated head trauma is influenced by age, inherited factors such as ApoE e4, and cumulative exposure to head contact.

Jordan et al. (16) came to similar conclusions in their study of boxers. The boxers with higher exposure (defined by number of bouts) had significantly higher chronic brain injury scores than those with low exposure. Boxers with low exposure had low chronic brain injury scores irrespective of ApoE e4 allele genotype, whereas those with high exposure and the ApoE e4 allele had higher chronic brain injury scores than boxers with high exposure and no ApoE e4 allele. Possession of the ApoE e4 allele was associated with an increased severity of neurological deficits in the high-exposure boxers.

To our knowledge, our study is unique in evaluating the risk of recurrent mild TBI in the development of later-life memory disorders and MCI. These data describe a significant association between recurrent concussion and MCI, as well as with self-reported memory impairments confirmed by a spouse or close relative. Retired professional football players with three or more concussions were twice as likely to be

diagnosed with MCI as those with one or two previous concussions, and five times more likely than those with no previous concussions. This trend continued with respect to selfreported significant memory problems. These findings suggest that the clinical features of dementia-related syndromes, such as reductions in synaptic density, loss of neurons, and granulovacuolar degeneration, may be initiated by repetitive cerebral concussions. Other recent peer-reviewed studies of recurrent concussion have identified an acute cumulative effect of concussion as measured by increased symptomatology or slowed recovery on symptom checklists and neuropsychological tests after subsequent injuries in high school and collegiate athletes (4, 10, 11, 14). These acute or short-term consequences of recurrent concussion should be of great interest to the sports medicine community, especially given that they parallel our findings of more chronic consequences after years of playing football.

Our study is influenced by the limitations of any retrospective self-report study. The study is limited by the uncertainty of how well the retired players recalled the concussions sustained during their careers and the accuracy of reporting memory problems and diagnosis of MCI. Recent literature has reported selective preservation of older information in subjects with AD-related dementia, which suggests that recollection of events involving previous injuries is not unlikely in these retired athletes (34). The purpose of the spouse or close relative questionnaire was to confirm the retired players' memory status and any physiciandiagnosed MCI. For cases in which there was disagreement in the responses of the retiree and the spouse or relative, phone calls and medical records were used to confirm the diagnosis. When the difference in responses could not be reconciled, the case was eliminated from the analyses. Another limitation of our study is that we do not currently know the ApoE allele form of these retired players, which might help to better understand some of these relationships.

CONCLUSIONS

Despite the limitations, these data suggest some very interesting findings—that a history of recurrent concussions, and probably sub-concussive contacts to the head, may be risk factors for the expression of late-life memory impairment, MCI, and AD. Our findings demonstrate a dose-response relationship between concussion and an increased lifetime burden; however, prospective longitudinal cohort studies are necessary to determine causality. Future prospective studies should implement genetic testing, more rigorous diagnostic criteria, historical documentation, and extensive serial evaluations (e.g., neuropsychological testing, functional neuroimaging) to clarify the direct or mitigating effects of concussion on lifetime risk of dementia or other neurological disorders.

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Acknowledgments

We thank Ron Brookmeyer, Ph.D., of the Johns Hopkins University, for providing data on the projected prevalence of Alzheimer's disease in the general American population.

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COMMENTS

The significance of repeated concussions is a question of great interest to all athletes, from players in grade schools to professionals. Anecdotes suggest that repetitive concussions may have a detrimental effect, but more rigorous analyses of this question have been less conclusive. In this report, Dr. Guskiewicz et al. surveyed retired professional football players, first by asking them to complete a general health questionnaire and subsequently by sending them a second questionnaire focusing on memory problems and cognitive impairment. Their data suggest that recurrent concussions seem to be related to mild cognitive impairment diagnosed by a physician and to be related to self-reported memory problems. These associations seemed to be stronger in patients with three or more reported concussions. Alzheimer's disease may have occurred at an earlier age in former National Football League players than in the population as a whole, but the number of patients with this diagnosis was quite small.

Like all retrospective studies that rely upon self-reported medical histories and health problems, this one is subject to bias in the accuracy with which problems were recalled and reported. Nevertheless, these results are of considerable interest. The authors make appropriate recommendations for further prospective studies to include such factors as genetic testing, standardized diagnostic criteria, and more extensive evaluation of players with concussion, perhaps including neuropsychological testing and functional neuroimaging.

Alex B. Valadka Houston, Texas

The safety of contact sports and likelihood of neurologic impairment occurring after retiring from the sport are of obvious concern to athletes and to parents deciding on which sports they should allow their kids to participate in. Studies such as this have the potential to provide important information in this regard. Unfortunately, this particular study is confounded by a critical design flaw of relying on retired athletes to accurately recall events from decades earlier and relating those events to their current memory problems. The study would have been much stronger had the authors corroborated the frequency and severity of concussions sustained with independent sources.

Donald Marion

Boston, Massachusetts

Thank you for the opportunity to comment on this excellent and extremely important study. The authors have used the tremendous resource of a database of the National Football League Retired Players Association, which contains 3683 individuals who played football at a high level for an average of 15 years (minimum six yrs of professional-level football). Using carefully constructed retrospective questionnaires, they have shown a strong association between three or more concussions sustained during a players' professional football career and mild cognitive impairment.

Although this evidence was the most compelling, they also showed an earlier onset and increased incidence of Alzheimer's disease in this group of professional football players who received concussions frequently than in the general age-matched male population in the United States.

This study has important and far-reaching implications. To my knowledge, this is one of few studies to show a positive association between repetitive concussion and long-term cognitive impairment and Alzheimer's disease (1–4). Therefore, this study documents the

dangers of contact sports, such as professional football. As professional football evolves, the speed of the plays appears to be increasing, the prowess, strength, and size of the athletes is measurably increasing, and, therefore, the potential for concussions, especially higher-impact energy concussions, is increasing. It is important to know whether the incidence of multiple concussions per player each year is increasing over time, and this invaluable cohort provides such details by including players with a history as far back as pre-World War II.

What are the implications for the future of the game? Possibly, rules could be tightened to limit the types of dangerous plays, but, in the "heat of the game," this may be unlikely. Helmet design has evolved tremendously in recent years (3), and clearly, studies with kinematic accelerometers of the type used in crash-test dummies by the auto industry should be performed and correlated with the "action replays," which are such an exciting facet of modern televised football. In this way, it may be possible to modify the game in ways that are compatible with increased safety without decreasing the spectator appeal of the game. New types of energy-absorbing foam and plastic are becoming available for football helmets.

However, as with professional boxing, athletes who undertake high-impact sports need to be fully and demonstrably informed of the risks that they undertake in pursuit of their vocation. This important study will provide a basis upon which players' associations and teams can formulate decisions.

Do the implications of these data go further? Many have called for apolipoprotein E genotyping of professional boxers to reduce the risk of precipitating Alzheimer's disease in apolipoprotein E e4 homozygous boxers. Should the same apply to professional football players, ice hockey players, and rugby players?

The authors have demonstrated that they have access to an enormous "data mine" to test the role of long-term physical fitness upon the development of delayed degenerative joint disease, low back disorders, and cardiovascular mortality. Do the cumulative effects of strains, sprains, and fractures, which are the inevitable consequence of professional football, outweigh the beneficial effect of many years of peak physical fitness upon the musculoskeletal system?

M.R. Ross Bullock Richmond, Virginia

Dr. Guskiewicz et al. have assessed by questionnaire a large number of retired professional football players to assess the incidence of concussions and more serious head injuries sustained during their playing careers and to determine whether such injuries influenced the subsequent development of Alzheimer's disease or mild cognitive impairment. Their results indicated that football players with repetitive concussion injuries (three or more) have a fivefold prevalence of mild cognitive impairment and a threefold increase in self-reported

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memory problems. The authors also suggest a 'soft' association between concussion and Alzheimer's disease.

This is an interesting paper that poses an intriguing hypothesis regarding the consequences of recurrent concussion, not only to create short-term problems, but also to accelerate the decline of cognitive function in later years. While tantalizing, the findings are soft. This data is derived from a questionnaire administered to a group that may have substantial bias, especially considering the recent reports and concerns expressed by physicians and the media. How did the authors pare down the original 2552 respondents to 758 whose memory questionnaires were analyzed? Figure one suggests an earlier onset of Alzheimer's disease in respondents aged less than 69 years, but the trend corrects by the age of 75. If the hypothesis is correct, why shouldn't this early separation persist or widen over time?

As usual, the data in sports medicine is difficult to control. Despite its shortcomings, it is reasonable that this paper should be published, not on the basis of its science, but on its conjecture and the need for neurosurgeons to be more aware of the current information in this area.

> Arthur L. Day Boston, Massachusetts

his latest manuscript on the relationship between cognitive impairment and recurrent concussion focuses on players from the National Football League. As in previous studies, there is an association between the frequency of recurrent concussion, the development of mild cognitive impairment, and the suggestion that Alzheimer's disease develops earlier in such patients. This trend is potentially of interest, but a larger sample is necessary.

One concern with the manuscript is the lack of controls in other sports where aggressive behavior is common but concussion is relatively rare, such as in wrestling. There may be genetic linkage to aggressive behavior and cognitive impairment later in life, which is separate from concussion. Perhaps the link is unlikely, but such controls in future studies would help support the hypothesis. Clearly, this is an area of continuing interest and the authors work is important.

> Lawrence F. Marshall San Diego, California

Infortunately, this manuscript reflects the low priority our society places on the prevention of head injuries and the major sequelae. It attempts to address the significant concern that repeated head injury leads to brain damage. Injury prevention programs, such as ThinkFirst, confront the lack of accurate studies on the potential damage of head trauma such as those sustained by both amateur and professional athletes.

The present study does not dispel uncertainties regarding the relationship between repeated concussions and subsequent onset of brain disorders, most importantly Alzheimer's disease. The study suffers from lack of professionally obtained prospective data. The glaring

deficiency of this study is its reliance on questionnaires from patients and relatives that were obtained retrospectively. Society must provide the author with the necessary funds and incentive to do the study correctly based on professionally obtained prospective data. Regrettably, the questions raised by the authors are of great importance to society and remain unanswered.

> Charles H. Tator Toronto, Ontario, Canada

his is an extremely valuable contribution. Most concussion studies focus on the days and weeks following the injury with the implicit assumption that recovery to preinjury levels is the end of the issue. The present paper provides strong suggestion that some residua of a concussion may not become manifest until decades after the injury. The study also provides a strong rationale for future studies focusing on the effects of concussion on cognitive reserves, rather than simply on performance in the immediate aftermath of injury. Moreover, because the present study demonstrates a dose-response relation between concussion and future cognitive disorder, it highlights the importance of reducing lifetime burden of concussion in athletes.

The authors are to be commended for clearly stating the limitations of their retrospective self-report experimental design. However, the 'gold-standard' methodology would require a multi-decade prospective study. While I think the present findings support the need for a prospective inception-cohort study on this question, this should not overshadow the importance of the present findings and the importance of additional follow-up studies exploring the pathophysiological underpinnings of the present findings.

> Joseph Bleiberg Neuropsychologist Washington, D.C.

This is an important paper on the relationship between cerebral concussion and subsequent cognitive impairment in retired professional football players. Its major flaw, as the authors acknowledge, is that the history of previous concussion was based on the players' 'retrospective recall of injury events.' Nonetheless, their data strongly suggests there is a cumulative deleterious effect of repeated concussion on later cognitive function. It further emphasizes the need to enhance protective measures that minimize concussion in contact sports and to carefully follow players by documenting the number and severity of concussive events throughout their careers. Finally, given the increasing data concerning the long-term risk of greater cognitive impairment for concussed individuals carrying the apolipoprotein E e4 allele, genetic screening and counseling of individuals about to embark on a potentially long career of contact sports should be considered.

> Daniel F. Kelly Los Angeles, California



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EXHIBIT 56

CHRONIC TRAUMATIC ENCEPHALOPATHY IN A NATIONAL FOOTBALL LEAGUE PLAYER

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Received, August 30, 2004. Accepted, February 10, 2005. **OBJECTIVE:** We present the results of the autopsy of a retired professional football player that revealed neuropathological changes consistent with long-term repetitive concussive brain injury. This case draws attention to the need for further studies in the cohort of retired National Football League players to elucidate the neuropathological sequelae of repeated mild traumatic brain injury in professional football.

METHODS: The patient's premortem medical history included symptoms of cognitive impairment, a mood disorder, and parkinsonian symptoms. There was no family history of Alzheimer's disease or any other head trauma outside football. A complete autopsy with a comprehensive neuropathological examination was performed on the retired National Football League player approximately 12 years after retirement. He died suddenly as a result of coronary atherosclerotic disease. Studies included determination of apolipoprotein E genotype.

RESULTS: Autopsy confirmed the presence of coronary atherosclerotic disease with dilated cardiomyopathy. The brain demonstrated no cortical atrophy, cortical contusion, hemorrhage, or infarcts. The substantia nigra revealed mild pallor with mild dropout of pigmented neurons. There was mild neuronal dropout in the frontal, parietal, and temporal neocortex. Chronic traumatic encephalopathy was evident with many diffuse amyloid plaques as well as sparse neurofibrillary tangles and τ -positive neuritic threads in neocortical areas. There were no neurofibrillary tangles or neuropil threads in the hippocampus or entorhinal cortex. Lewy bodies were absent. The apolipoprotein E genotype was E3/E3.

CONCLUSION: This case highlights potential long-term neurodegenerative outcomes in retired professional National Football League players subjected to repeated mild traumatic brain injury. The prevalence and pathoetiological mechanisms of these possible adverse long-term outcomes and their relation to duration of years of playing football have not been sufficiently studied. We recommend comprehensive clinical and forensic approaches to understand and further elucidate this emergent professional sport hazard.

KEY WORDS: Chronic traumatic encephalopathy, National Football League, Retired professional football players

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everal professional players of the National Football League (NFL) have retired prematurely because of postconcussion syndrome (29), a possible outcome of repeated concussion of the brain. The NFL Committee on Mild Traumatic Brain Injury, which was formed in 1994 to study this trend, has replaced the terminology postconcussion syndrome with mild traumatic brain injury (MTBI). MTBI is defined as a "traumatically induced alteration in brain function that is manifested by a) alteration of awareness or consciousness, including but not limited to loss of consciousness, sensation of being dazed or stunned, sensation of wooziness or fogginess, seizure, or amnesic period; and b) signs and symptoms commonly associated with postconcussion syndrome, including persistent headaches, vertigo, lightheadedness, loss of balance, unsteadiness, syncope, near-syncope, cognitive dysfunction, memory disturbance, hearing loss, tinnitus, blurred vision, diplopia, visual loss, personality change, drowsiness, lethargy, fatigue, and inability to

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perform usual daily activities" (29). In 1995, the committee recommended that the NFL should fund independent scientific research to understand the causes of MTBI and elucidate ways of preventing MTBI. Despite this recommendation, which was made many years ago, the possible long-term cognitive and neurodegenerative sequelae of professional football as well as the underlying histological changes and pathobiological cascades associated with and likely induced by the trauma of professional football are little understood. This is especially true for the neuropathological changes, because no cases have come to autopsy.

We herein report the first documented case of long-term neurodegenerative changes in a retired professional NFL player consistent with chronic traumatic encephalopathy (CTE). This case draws attention to a disease that remains inadequately studied in the cohort of professional football players, with unknown true prevalence rates. Although clinical assessments can determine encephalopathy and dementia, and new neuroimaging methods may aid in the detection of amyloid plaques (23), autopsy examination is required to confirm the neuropathological basis of these changes. Autopsies aimed at diagnosing long-term central nervous system (CNS) sequelae of repeated brain concussions in NFL players are virtually nonexistent. Our case represents an extremely rare scenario whereby a complete autopsy was performed on a retired NFL player with a comprehensive neuropathological examination, which revealed changes consistent with CTE.

CASE REPORT

Premortem History

Our patient was a 50-year-old professional football player who died approximately 12 years after retirement from the NFL. He began playing football in high school and played for 3 years in college, where he was a team's most valuable player and a multiyear starter as a lineman in a Division I college. Drafted into the NFL at the age of 22 years, he played in 245 games in the NFL during 17 seasons. For 10 of those years, he played 177 consecutive games, principally as an offensive linesman. He was in the starting lineup in 150 consecutive games and played in 19 playoff games (15). After his retirement, he presented with a medical history that included atrial fibrillation and coronary atherosclerotic disease, which were treated with intraluminal stenting. Telephone interviews of surviving family members revealed a neuropsychiatric history that resembled a dysthymic disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (2). Other medical history included a deficit in memory and judgment as well as parkinsonian symptoms. He died suddenly from clinically documented myocardial infarction. There was no known history of brain trauma outside professional football.

Autopsy Findings

General

External examination revealed the body of an adult Caucasian man who weighed 244 lb and measured 69 inches (body mass index, 36 kg/m² [Class II obesity]). There was no external evidence of recent trauma. The pericardium revealed diffuse fibrocalcific and adhesive pericardioepicarditis. The cardiovascular system revealed dilated cardiomyopathy with severe cardiomegaly (855 g), severe bilateral atrioventricular dilation; biventricular hypertrophy; and patchy subendocardial, endocardial, and valvular fibrosis. There was evidence of cardiogenic shock with centrilobular hepatocellular coagulative necrosis. There was chronic sinusoidal hepatic congestion with trabecular atrophy. There was severe atherosclerosis of the proximal and distal right coronary artery and the left anterior descending coronary artery, with approximately 95% multifocal intraluminal occlusion. The proximal left circumflex coronary artery revealed moderate atherosclerosis with 50 to 75% focal intraluminal occlusion. A metal intraluminal surgical stent was identified in the proximal right coronary artery. The myocardium revealed moderate interstitial and perivascular fibrosis. The respiratory system revealed moderate acute pulmonary edema and congestion with patchy, acute, and terminal bronchopneumonia.

Gross CNS Findings

The dura mater and dural sinuses appeared unremarkable. The formalin-fixed whole brain weighed 1565 g, whereas the cerebellum and brainstem weighed 220 g. The leptomeninges were unremarkable. There was no cerebral atrophy. There were no cortical contusions, infarcts, or hemorrhages. There was moderate cerebral edema but no evidence of uncal or cerebellar tonsillar herniation. The cerebral blood vessels and circle of Willis revealed focal mild eccentric atherosclerosis of the left vertebral artery without aneurysms or other anomalies. The cranial nerves were normal.

Coronal sections of the cerebral hemispheres revealed no significant gross pathological changes of the cortex, white matter, or deep gray structures. The ventricles were not enlarged, and there was no atrophy of the hippocampi or the corpus callosum. The amygdala and piriform cortex demonstrated no atrophy. The mamillary bodies and hypothalamus appeared unremarkable.

The midbrain, pons, and medulla oblongata were grossly unremarkable, except for the pigmentation of the substantia nigra, which was attenuated for age, but the locus ceruleus appeared adequately pigmented. There were no infarcts in the cerebellum. There was mild atrophy of the anterior superior vermis. The dentate nucleus appeared normal. The pituitary gland and spinal cord were unremarkable.

CNS Histomorphology

Primary hematoxylin and eosin stains were performed on all tissue sections. After they were reviewed, a panel of spe-

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cialized histochemical and immunohistochemical stains was applied. These specialized stains included β -amyloid protein (Beta-A4; Dako, Carpinteria, CA), neurofilament (Dako), α-synuclein (Zymed Laboratories, South San Francisco, CA), and τ-protein (Dako) immunostains as well as Bielschowsky's silver impregnation histochemical stains.

The frontal, parietal, and temporal neocortex revealed normal laminar and columnar organization, with mild neuronal dropout and astrogliosis. The penetrating parenchymal vessels revealed patchy perivascular hemosiderin-laden macrophages in the Virchow-Robin spaces. There was moderate cerebral edema. The centrum semiovale revealed no white matter rarefaction or perivascular pallor but demonstrated focal mural mineralization of deep penetrating blood vessels. There was no periventricular leukomalacia, and the subependymal white matter was nongliotic. The basal ganglia and subcortical white matter tracts were unremarkable. There was mild to moderate neuronal dropout of the nigral pars compacta and pars reticularis, accompanied by mild extraneuronal pigment and astrogliosis. There were no Lewy bodies. There was no mineralization of pallidal vessel walls. The hippocampus revealed mild neuronal dropout of the pyramidal neurons of Sommer's sector (CA-1) without selective neuronal necrosis. There were no Hirano bodies and no granulovacuolar neuronal degeneration. The subiculum, entorhinal cortex, and alveus were unremarkable, as were the amygdala and basal nucleus of Meynert. There were no lesions in the remaining brainstem structures. The cerebellar cortex revealed mild neuronal dropout and Bergmann astrogliosis of the Purkinje cell layer. This was accentuated in the superior anterior vermis, which also revealed mild atrophy of the internal granule cell layer. The cerebellar white matter and dentate nucleus were unremarkable. The adenohypophysis and neurohypophysis were normal. The cervical, thoracic, and lumbar segments of the spinal medulla were normal and demonstrated no signs of anterior horn cell dropout or degenerative changes.

Specialized Stains

The battery of immunohistochemical stains revealed frequent diffuse extracellular amyloid plaques (Fig. 1A), sparse τ-positive neuritic threads (Fig. 1B), and sparse intraneuronal band-shaped and flame-shaped neurofibrillary tangles (NFTs) (Fig. 1C) in the frontal, temporal, parietal, occipital, and cingulate cortex and the insula. Cortical Lewy bodies were absent. Many neocortical perikarya revealed diffuse cytoplasmic immunopositivity for neurofilament protein. The hippocampal formation was spared of these pathological changes; the dentate gyrus, cornu ammonis, and subiculum demonstrated no diffuse amyloid plaques (Fig. 1D), NFTs, neuritic threads, or Lewy bodies. The subcortical nuclei and brainstem, including the substantia nigra, contained no diffuse amyloid plaques, NFTs, neuritic threads, or Lewy bodies. There was no histological evidence of cerebral amyloid angiopathy.

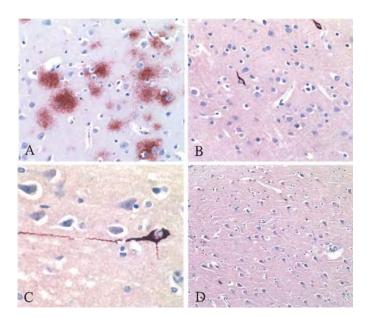


FIGURE 1. A, β-amyloid immunostain of the neocortex (original magnification, ×200) showing frequent diffuse amyloid plaques. B, τ immunostain of the neocortex (original magnification, ×200) showing sparse NFTs and many τ-positive neuritic threads. C, τ immunostain (original magnification, ×400) showing an NFT in a neocortical neuron with extending τ-positive dendritic processes. D, β-amyloid immunostain (original magnification, ×100) of the Sommer's sector (CA-1 region of the hippocampus) showing no diffuse amyloid plaques.

Apolipoprotein $E(\epsilon)$ Genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from 25-mg formaldehyde-fixed brain tissue with the QIAamp DNA Mini Kit (Qiagen, Valencia, CA) using the protocol for isolation of genomic DNA from formaldehyde-fixed tissues. Representative whole-genome amplification of the extracted DNA was accomplished using the GenomiPhi DNA Amplification Kit (Amersham Biosciences, Piscataway, NJ). Restriction fragment length polymorphism analysis was completed using previously published protocols (20). The genotype of the sample was determined to be E3/E3 (Fig. 2).

DISCUSSION

Although head injury (repeated mild concussive brain injury or a single episode of severe diffuse brain injury) may increase the risk of sporadic Alzheimer's disease (AD), (14, 25) importantly, this case did not meet criteria for AD but met criteria for CTE. Cortical amyloid plaques and NFTs were unaccompanied by tangles in the entorhinal cortex or hippocampus, which is the usual starting point for neuropathological changes of sporadic AD. The first neuropathological report on the long-term effects of contact sport (boxing) was written by Brandenburg and Hallervorden (8) in 1954, in a 51-year-old retired boxer who manifested delayed posttraumatic dementia with AD pathological changes. In 1973,

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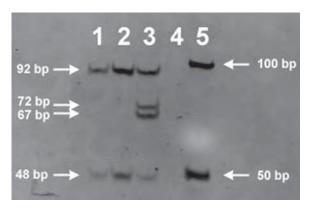


FIGURE 2. Polyacrylamide gel electrophoresis showing DNA from decedent's brain under ultraviolet light. Lanes 1 and 2 contain duplicate samples of the DNA extracted from the brain sample amplified as described in the text and digested with HhaI to reveal the restriction fragment length polymorphism. Lane 3 is a sample known to be E2/E4 prepared in parallel with the samples from Lanes 1 and 2. Lane 4 is a negative template control. Lane 5 contains a 50- to 2000 base-pair (bp) ladder.

Corsellis et al. (8) described the neurohistological substrate of CTE in the brains of 15 retired professional and amateur boxers. These reports and other subsequent reports (12-14, 34-36, 39, 41) have described characteristic neuropathological findings for CTE, especially in boxers, which comprise: 1) sparse to many *τ*-positive NFTs in the neocortex concentrated around penetrating parenchymal vessels, 2) neocortical τ-immunopositive neurites in the neuropil (neuropil threads), and 3) neocortical diffuse amyloid plaques with or without neuritic plaques. Neocortical changes seem to spare the hippocampus. The NFT distribution is notably different from that observed in normal aging and AD, in which there is early involvement of the entorhinal cortex and hippocampus with later involvement of the neocortex in advanced stages. Other reported delayed gross neuropathological changes in the brains of retired boxers have included cerebral atrophy, cerebral amyloid angiopathy, communicating hydrocephalus, fenestrations of the septum pellucidum, cavum septi pellucidi, cerebellar cortical atrophy, and degeneration of the substantia nigra (8, 10, 12, 34, 38, 39, 41). After an extensive search of the medical literature, we could not identify any study on the neuropathological substrate of delayed neurodegeneration in professional football players.

The pathological mechanisms for these delayed posttraumatic changes are thought to be biochemical cascades that are induced by cumulative effects of repeated low-grade concussive brain injury, especially changes like hyperphosphorylation of neuronal microtubule-associated protein and aberrant metabolism of amyloid precursor protein (13, 34, 38, 39). It has been suggested that repeated axonal injury, vascular injury, and ischemia trigger a cascade of molecular events involving derangement of neuronal cytoskeletal metabolism and accumulation of abnormal cytoskeletal proteins; increased expression of amyloid precursor protein; and a subsequent increase in the β -amyloid fragment, which is deposited in amyloid plaques.

The sport of American football has a high probability of impact to the head and concussion of the brain. There are up to 300,000 cases per year of MTBI or brain concussion in contact sports in the United States (29-32). There are approximately 0.41 concussions per NFL game of American football: 67.7% of concussions involve impact by another player's helmet, 20.9% involve impact by other body regions (e.g., a knee), and 11.4% involve impact on the ground (29, 31, 32, 40). It has been reported that 9.3% of the concussions involved loss of consciousness and 2.4% of the concussions resulted in hospitalization. Most (92%) of the players who sustain a concussion return to practice in less than 7 days; fewer (69%) of the players who experience loss of consciousness return to practice in less than 7 days. The relative risk of brain concussion in NFL players is associated with player position. Although every player position is at risk of brain concussion, quarterbacks, wide receivers, tight ends, and defensive backs have the highest relative risks (1.62, 1.23, 0.94, and 0.93 concussions per 100 games, respectively) (30-32). The most frequent position played by the patient was an offensive lineman. In a 17-year career as an offensive lineman, he sustained numerous episodes of mild traumatic and/or concussive brain injury, which is supported by the histological evidence of remote hemorrhages into the Virchow-Robin spaces of penetrating parenchymal vessels, with multiple perivascular hemosiderin-laden macrophages. These histological findings indicate microvascular injury that may be sustained from repetitive concussive brain injury.

Concussions in professional football are related to translational acceleration-deceleration, with considerable head impact velocity and velocity changes. The injury potential of these transferring inertial forces is ameliorated by the use of protective helmets. Since 1978, there has been a remarkable reduction in fatal head injuries (51%), concussions (35%), and cranial fractures (65%) in youth football, after the voluntary adoption of set standards for protective helmet manufacturers by the National Operating Committee on Standards for Athletic Equipment (29, 31, 32). The NFL has aggressively pursued the prevention of traumatic brain injury during play by the modification of play and rules of play as well as the introduction of improved standardized helmets, which have generated a marked reduction in the incidence of fatal and nonfatal head injuries (6). Although the technology and safety of football helmets have advanced in the past decades, this player's career spanned earlier decades in which helmets were not as protective as the ones in use today.

The acute sequelae of brain injury in professional football players have been elucidated and ameliorated, although there is less information about the chronic long-term sequelae of brain injury in retired football players. A variety of delayed clinical outcomes have been studied by radiological and neuropsychiatric testing, although without neuropathological evaluation. Such studies have suggested long-term impaired cognitive functioning (memory, planning, and visuoperceptual processing), electroencephalographic abnormalities, and cerebral atrophy in professional boxers, soccer players, football players, ice hockey players, karate players, lacrosse players, and rugby players (1, 3, 5, 7, 11, 22, 24, 33, 39, 42, 43). Possible symptoms of CTE may include recurrent headaches,

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irritability, dizziness, lack of concentration, impaired memory, and mental slowing; mood disorders, explosive behavior, morbid jealousy, and pathological intoxication and paranoia; tremor, dysarthria, and parkinsonian movement disorders (9, 18, 19, 26, 37). Postmortem telephone interviews of close family members of the patient in this case indicated a longstanding mood disorder that resembled a dysthymic disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (2).

Apolipoprotein E (ϵ) and CTE

We analyzed the apolipoprotein E (APOE) genotype of the patient in this case, because genotypic variation of APOE predisposes to or mitigates the development of AD and posttraumatic AD-like pathological changes (4, 16). The possession of the APOE4 allele by professional football players and boxers has been associated with chronic neurological deficits, lower scores in overall cognitive performance, and lower scores in cognitive domains (17, 21). The three APOE isoforms differ by only one or two amino acids but confer a three- to ninefold increase in the risk for developing these diseases (APOE4 > APOE3 > APOE2). Individuals who inherit one or two copies of APOE4 have an earlier age of onset for late-onset and sporadic AD and increased long-term sequelae of brain trauma (4). The presence of the APOE4 allele does not confer absolute predisposition to CTE and/or other sporadic or posttraumatic AD pathological changes, and absence of the APOE4 allele does not confer absolute protection from these diseases (4). Geddes et al. (12) reported the E3/E3 APOE genotype in two patients with repetitive head injury in contact sports who demonstrated neuronal cytoskeletal changes and CTE. The authors concluded that CTE can occur in the absence of APOE4 (12, 13). Our finding of the E3/E3 APOE genotype in our patient appears similar to the findings in the cases reported by Geddes et al. (12, 13).

CONCLUSION

This case study by itself cannot confirm a causal link between professional football and CTE. However, it indicates the need for comprehensive cognitive and autopsy-based research on longterm postneurotraumatic sequelae of professional American football. Empirical, cognitive, and postmortem data on CTE are currently unavailable in the population cohort of professional NFL players. Our report therefore constitutes a forensic epidemiological sentinel case that draws attention to a possibly more prevalent yet unrecognized disease because of the rarity of CNStargeted autopsies in the cohort of retired NFL players.

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COMMENTS

This is the first publication of chronic traumatic encephalopathy (CTE) in a retired National Football League (NFL) player. It should come as no surprise, though, as a number of NFL players have had to retire from sequelae of multiple mild traumatic brain injuries. It also is consistent with the findings of studies of Kevin Guskiewicz, Julian Bailes, and others at The Center for the Study of Retired Athletes at the University of North Carolina. These researchers found retired NFL players with three or more concussions had a fivefold prevalence toward mild cognitive impairment and a threefold prevalence toward significant memory problems compared with retirees with no history of concussion. Hopefully, in the years ahead, the center will be able to study these retirees so a better idea of the incidence of CTE in former NFL players becomes known, as well as how many years of participation may lead to this risk. I fully support the conclusions of Omalu et al.

Robert C. Cantu Concord, Massachusetts

In this case report of CTE in a retired NFL player, the authors provide an in-depth description of the deceased player's neuropathological findings. The authors assert that the individual's premortem cognitive decline, depression, parkinsonian symptoms, and neuropathological findings were a manifestation of traumatic encephalopathy resulting from his many years of professional football. Although this is an interesting hypothesis and it is

likely he sustained several mild traumatic brain injuries over the course of his NFL career, this assertion appears to be somewhat presumptuous because they are only reporting associated findings in a single individual. It is notable that no mention is made of any concussions, mild or otherwise, in his premortem history, and that he played predominantly as an offensive linesman which is one of the player positions associated with the lowest frequency of concussion in the NFL. Additionally, this individual's apolipoprotein E genotype was not E4 which has been more strongly associated with the development of Alzheimer's disease. Ideally, the causal link suggested here between a career in professional football and CTE would result from postmortem assessments of a group of similar individuals from the NFL compared with another group of otherwise well-matched individuals whose careers did not involve repetitive contact sports. I encourage the authors to continue their investigations.

Daniel F. Kelly

Los Angeles, California

The authors provide a detailed analysis of the central nervous system histopathology in an offensive lineman who played for 17 seasons in the NFL and died from a myocardial infarction 12 years after retirement. The autopsy findings were consistent with CTE. This article complements the series of articles by Pellman et al. that have previously appeared in this journal regarding the neuropsychological abnormalities suffered by NFL players, and provides an important anatomic underpinning for those abnormalities. Unfortunately, Omalu et al. did not provide specific information about the neuropsychological deficits experienced by this athlete, other than to state that he met criteria for dysthymic disorder, had deficits in memory and judgment, and had parkinsonian symptoms. It is unlikely that detailed neuropsychological testing was routinely performed during his career, so such data was probably not available. The increasing use of detailed pre- and post-traumatic neuropsychological testing by the NFL and amateur football groups should provide an invaluable database of information that will allow for clinicalanatomic correlations not previously possible. Together with information obtained from functional magnetic resonance imaging studies, this data will significantly advance our understanding of the cellular and physiologic mechanisms of traumatic brain injury.

Donald W. Marion *Boston, Massachusetts*

This article raises some interesting questions. However, in this case report, the scientific validity of the putative association between suspected repetitive mild traumatic brain injury in professional football players and histological findings consistent with chronic neuro-degenerative processes is, at the very least, questionable. This report highlights the potential value of a prospectively administered database that might include athletes' medical histories and, when available, postmortem findings and results of cognitive testing. More abundant and more rigorously collected data of this type might enable us to provide better answers to the questions posed here.

Alex B. Valadka Houston, Texas

malu et al. have added to our knowledge of neuropathological correlates of sports-related head injury. They provide a detailed postmortem analysis of a retired player who spent 17 years in the NFL. It is clear that we are just beginning to understand the myriad of biomechanical, physiological, neurogenetic, and neurocognitive sequelae of this condition. By providing the first reported case of autopsy-confirmed traumatic encephalopathy in a professional football player, these authors provide an initial

OMALU ET AL.

window to structural changes of this condition. It is noted that the authors indicate that the player's encephalopathy occurred as a result of long-term repetitive concussive brain injury. However, they did not indicate the frequency of concussive events or the numbers of years over which concussive events occurred. Because concussive events were not recorded systematically at the time of this player's career, we cannot be sure that his encephalopathy was caused by either repetitive or long-term events.

> Kenneth C. Kutner Neuropsychologist Hackensack, New Jersey

malu et al. have reported a sentinel case of a 50-year-old retired NFL player with 17 years experience as a professional football player. It provides a glimpse, for the first time, into the gross and microscopic pathological changes of this relatively young brain, which had extensive exposure to repetitive head impacts in football. These findings, which are not consistent with Alzheimer's disease or aging, but rather CTE, have been observed previously in autopsy material of retired boxers. These consist predominantly of markers of neuronal and axonal injury to the neocortex with relative sparing of the hippocampus, as well as hemorrhagic markers in the Virchow Robin spaces.

Despite attempts to enact rule changes and to improve helmet design, naturally there are still regular episodes of traumatic brain injury in contact sports such as football. Irrespective of design modifications in the football helmet, there still exists the regular occurrence of rapid acceleration-deceleration mechanisms of brain injury which are difficult to ameliorate or eliminate. In addition, recent reports have suggested that the true incidence of concussion in football, recognized or subclinical in nature, is higher than previously believed. Although earlier research has shown that contact athletes may later develop mental and cognitive impairment, this case report documents cerebral histopathological abnormalities and adds to our knowledge as we further study the long-term consequences of repetitive traumatic brain injury.

Julian E. Bailes

Morgantown, West Virginia

his article raises controversial questions concerning the potential risk of CTE in retired NFL players. The authors provide detailed and compelling neuropathological evidence supporting the presence of CTE in this particular case, but there is no documentation of concussion history during the athlete's sports career. As the authors openly note, this is a single case report and does not establish an empirically substantiated causal relation between participation in professional football and the development of CTE, even if previous concussion history had been recorded in this case. Clearly, further investigation with multiple subjects and a controlled experimental design is needed.

By reporting their case, the authors lay a solid groundwork for pursuing further neuropathology studies in professional football players. Based on the potential association between CTE and boxing, it is certainly conceivable that there is a link between the activities inherent in professional football and CTE. However, the rate at which a typical player sustains head injuries and the severity of those injuries are important factors that may differentially affect the likelihood of developing CTE. Thus, it will be important to note not only the length of career and the number of athlete exposures, but to also include reliable concussion history data in future studies. Empirical studies that include this information would portray a more complete picture of the risks of professional football, contribute knowledge of the possible etiologic factors of CTE, and convey precautionary measures, if needed, to minimize its occurrence.

The postmortem finding of CTE in a retired football player raises

the possibility that some of the cognitive, emotional, and neurological symptoms observed in retired NFL athletes may be manifestations of disease processes other than Alzheimer's disease, which has been more extensively documented in recent literature. The relation of CTE, Alzheimer's disease, and the Apolipoprotein E genotype in retired athletes is also fuel for future research. Although this article raises more questions than it answers, it provides a foundation indicating that these questions are important and worth pursuing.

Joseph Bleiberg

Neuropsychologist Washington, District of Columbia

his article represents the first documented case of long-term neurodegenerative changes in a retired professional NFL player. The case report describes the comprehensive autopsy and laboratory findings of a retired professional football player showing neuropathological changes consistent with long-term repetitive concussive brain injury. The report states that the deceased athlete "sustained numerous episodes of mild traumatic and concussive brain injury..." during his 17-year career as an offensive lineman. Although the report does not indicate an approximate number of suspected concussions, we are left to assume that it was well above the average of two concussions reported to the Center for the Study of Retired Athletes by retired NFL players with an average of 6.5 years in the league (1). Given that the deceased athlete played approximately three times longer than the retired NFL players in that study, we might predict that he experienced at least six concussions, and probably many more subconcussive impacts to the head during his professional football career.

The authors indicate that the deceased player demonstrated longstanding mood disorders that resembled a dysthymic disorder. This report parallels findings from the Center for the Study of Retired Athletes which suggest there is an association between recurrent concussions sustained during the professional playing years, and the likelihood of being diagnosed with clinical depression (1). As the authors state, the case study by itself cannot confirm a causal link between professional football and chronic neurodegenerative diseases such as CTE, however, it indicates the need for a more comprehensive study of both active and retired professional football players.

Furthermore, this case report calls to team physicians and athletic trainers for improved injury surveillance of concussions and other brain related traumas so future studies may be able to better understand the relationship between these injuries and the neurodegenerative changes described. For years there has been speculation of an increased risk for late life cognitive impairment in athletes with a history of multiple concussions. While this well written case report provides a good starting point for answering these important questions, future prospective studies implementing genetic testing, more rigorous diagnostic criteria, historical documentation, and extensive serial evaluations (e.g., neuropsychological testing and functional neuroimaging) will be necessary to clarify the direct or mitigating effects of head trauma on lifetime risk of such neurological disorders. The authors should be commended for providing the medical community with a very interesting paper that will make significant contributions to the literature on the topic of sport-related concussion and neurodegenerative disease, and will likely serve as an impetus for future study in this area.

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^{1.} http://www.csra.unc.edu/statistics.htm. Accessed June 13, 2005.

EXHIBIT 57

CHRONIC TRAUMATIC ENCEPHALOPATHY IN A NATIONAL FOOTBALL LEAGUE PLAYER: PART II

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OBJECTIVE: We present the second reported case of autopsy-confirmed chronic traumatic encephalopathy in a retired professional football player, with neuropathological features that differ from those of the first reported case. These differing pathological features underscore the need for further empirical elucidation of the pathoetiology and pathological cascades of long-term neurodegenerative sequelae of professional football.

METHODS: A psychological autopsy was performed with the next-of-kin and wife. Medical and hospital records were reviewed. A complete autopsy was accompanied by a comprehensive forensic neuropathological examination. Restriction fragment length polymorphism analysis was performed to determine apolipoprotein-E genotype.

RESULTS: Pertinent premortem history included a 14-year span of play in organized football starting from the age of 18 years. The subject was diagnosed with severe major depressive disorder without psychotic features after retirement, attempted suicide multiple times and finally committed suicide 12 years after retirement by ingestion of ethylene glycol. Autopsy revealed cardiomegaly, mild to moderate coronary artery disease, and evidence of acute ethylene glycol overdose. The brain showed no atrophy, a cavum septi pellucidi was present, and the substantia nigra showed mild pallor. The hippocampus and cerebellum were not atrophic. Amyloid plaques, cerebral amyloid angiopathy, and Lewy bodies were completely absent. Sparse to frequent τ -positive neurofibrillary tangles and neuropil threads were present in all regions of the brain. Tufted and thorn astrocytes, as well as astrocytic plaques, were absent. The apolipoprotein-E genotype was E3/E4.

CONCLUSION: Our first and second cases both had long careers without multiple recorded concussions. Both manifested Major Depressive Disorder after retirement. Amyloid plaques were present in the first case and completely absent in the second case. Both cases exhibited neurofibrillary tangles, neuropil threads, and coronary atherosclerotic disease. Apolipoprotein-E4 genotypes were different. Reasons for the contrasting features in these two cases are not clear. Further studies are needed to identify and define the neuropathological cascades of chronic traumatic encephalopathy in football players, which may form the basis for prophylaxis and therapeutics.

KEY WORDS: Chronic traumatic encephalopathy, National Football League, Professional football players

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n 2005, we reported the first autopsyconfirmed case of chronic traumatic encephalopathy (CTE) in a National Football League (NFL) player (5, 27). The brain in that report showed diffuse amyloid plaques, neuropil threads (NT) and neurofibrillary tangles (NFT) in the neocortex. There were no diffuse amyloid plaques, NTs, or NFTs in the entorhi-

nal cortex or hippocampus. We now report the second autopsy-confirmed case of CTE in another NFL player with neuropathological findings that are somewhat distinct from the initial reported case. In contrast to the first case, the brain in this second case revealed topographically distributed sparse to frequent NFT and NT in the neocortex, hippocampus,

subcortical ganglia, and brainstem. There were no diffuse amyloid plaques. Whereas the apolipoprotein-E (APOE) genotype of our first case was E3/E3, the APOE genotype of this second case was E3/E4.

Chronic neurodegenerative changes have been causally associated with contact sports, including boxing, soccer, and American football (7, 13–15, 39, 40, 43, 45, 53). Autopsies aimed at diagnosing CTE are virtually non-existent in active or retired NFL players. This has precluded definitive elucidation of pathological cascades of chronic neurodegenerative sequelae of professional football by direct tissue analyses. Since the 1995 recommendation of the NFL Committee on Mild Traumatic Brain Injury (MTBI) for the NFL to fund research into MTBI, significant progress has been made in understanding and ameliorating or preventing acute MTBI (28-37, 50-52). However, we currently know little regarding the chronic neurodegenerative outcomes of long-term play in professional football. The differing pathological findings in our two cases, especially the absence of amyloid plagues in the second case, underscore the urgent need for further information and possibly a prospective, longitudinal study of former professional football players. Such a study, combining neurological, neuropsychiatric, neuroimaging, and postmortem neuropathological facets and findings, might form the basis for possible prophylaxis and therapeutics.

Premortem History

A psychological autopsy of this 45-year-old African-American man was performed with his next-of-kin and wife. He had married twice and had no children. At the time of his death, he lived alone and was separated from his second wife. He enlisted in the United States Armed Forces in 1977 after high school and served for 2 years. He began playing football at the age of 18 years, while in the military, and played as an offensive tackle for 2 years. He entered college after military service and moved on to a college football scholarship, during which time he played as a starting offensive line tackle for 4 years (1980– 1984). In 1984, he was drafted by the NFL as a right guard and played for 8 consecutive years (1984-1992). He sustained several musculoskeletal and cartilage injuries while playing professional football, which necessitated multiple knee, elbow, and shoulder surgeries. He had indicated to his second wife that he sustained repeated mild concussions of his head on numerous occasions during his football career.

During his childhood and during his amateur and professional football career, his wife and family did not observe any obvious psychosocial or behavioral abnormality. However, within several years of his retirement from the NFL, his wife reported that he became increasingly quiet and that he was afraid and fearful, with paranoid tendencies. On some occasions, he would sweat profusely in public settings and become agitated when approached by other people. At other times, he was noted to exhibit a reassured, confident, and approachable demeanor. In private, he sometimes became extremely reclusive and distanced himself from all personal interactions with family and friends, often locking himself in the house for 1 to

2 days. He would later seek companionship from family and friends as if nothing had happened. He manifested unpredictable fluctuations in mood and personality.

Before his retirement, the decedent had started a sole proprietorship business in 1988. He began working as a sales manager for another business entity in 1992. In 1993, he formed a second wholesale produce corporation. In 1994, he diversified his business and expanded into food processing and manufacturing and created yet another new corporation. His business activities and decisions were regarded as extraordinarily risky, ambitious, and rather irrational. In business dealings, he also exhibited sudden and unexpected fluctuations in mood and personality. At some times, he appeared hard working, ambitious, and highly driven, but at others, he exhibited sudden bouts of agitation and irritability with no clear instigator. He would lose his ability to focus and concentrate and would become highly emotional, which led to failure of his business operations. In 2000, he further expanded his food service business and formed another sole proprietorship entity.

He was described by the next-of-kin as having "extreme highs and lows." He became progressively incapable of mentally handling very complex rational thoughts in matters of daily living and business. He became increasingly impulsive and paranoid. His erratic behavior continued to worsen; he exhibited disinhibition, began having financial problems, and could not sustain his businesses.

He began outpatient psychotherapy in 1992 after his first suicide attempt in 1991 by ingestion of rat poison and cold medications, after suspension from the NFL for violating the NFL's steroid policy. He was diagnosed with adjustment disorder with depressed mood after this first suicide attempt. He made several subsequent suicide attempts by ingestion of prescription drugs and antifreeze. He verbalized thoughts of suicide and attempted suicide again in 2003, shortly after he was investigated for a fire that destroyed his business. In 2005, he was indicted for arson and wrongful business transactions for apparently setting fire to his factory plant. His behavior became increasingly characterized by constant thoughts of suicide, and he was admitted for psychiatric treatment three times. A few weeks after his last discharge from the hospital, he was found lying on a couch with altered mental status; he died at a local hospital several hours later. Laboratory analyses of his blood and urine samples performed before his death revealed metabolic acidosis with increased blood lactic acid, negative base excess, high anion gap, high serum osmolality, hypocalcemia, and positive urine oxalate crystals.

There was no contributory family history relative to significant medical problems or severe depression/suicide attempts. There was a documented single episode of a rollover of a sport utility vehicle which he was driving when he swerved to avoid hitting a deer. He experienced a brief loss of consciousness at the scene, but recovered completely. There was at least one clinically documented severe concussive brain injury during play of football in 1987, which necessitated removal from play for at least 1 week. He was hospitalized for one night and complained of lightheadedness, unsteadiness in gait, and difficulty

concentrating. These symptoms were present for at least several days. Medical records from a local psychiatric hospital, where the decedent received follow-up psychiatric treatment, revealed a primary psychiatric diagnosis of major depressive disorder, which was severe and without psychotic features. Other significant medical history included thyroidectomy (2 mo before death) for hyperthyroidism (Grave's disease).

Relevant Findings on General Autopsy

A complete autopsy was performed at the Allegheny County Coroner's Office. External examination revealed a welldeveloped, well-nourished African-American man who weighed 275 pounds and measured 72 inches and seemed consistent with the stated age of 45 years. There was no evidence of recent blunt force, penetrating force, or projectile trauma. Internal examination revealed a heart weight of 580 g. The heart showed patchy myofibrillary hypertrophy with focal infiltration of the subendocardium by neutrophils. The coronary arteries showed mild to moderate eccentric, segmental atherosclerosis with 40 to 60% multifocal luminal occlusion. The lungs showed moderate acute pulmonary edema and congestion. The right and left kidneys appeared grossly unremarkable; however, numerous intratubular oxalate crystals were found in histology sections of the kidneys. Postmortem toxicological analyses of blood and urine revealed the presence of ethylene glycol in the urine, with a level of 460 mg/dl. There was no ethylene glycol detected in the blood (ethylene glycol has a short half-life, of 2.5–4.5 h).

Neuropathological Findings

The dura mater revealed no hemorrhages, xanthochromia, or subdural membranes. The brain weighed 1535 g in the fresh state. The cerebral and cerebellar hemispheres appeared symmetrical and revealed no anomalous gyral-sulcal convolutions, atrophy, contusions, infarcts, or hemorrhages. There was global edema and congestive swelling. The leptomeninges appeared normal, as did the vessels of the circle of Willis and the basilar and vertebral arteries. The cranial nerves were normal.

The neocortical gray ribbon was intact and the gray-white matter demarcation distinct. The centrum semiovale and the periventricular white matter revealed diffuse edema and congestion without hemorrhages, infarcts, or demyelination. The ventricles contained no abnormal fluid, were symmetrically compressed, and showed normal ependymal lining. A cavum septi pellucidi was present, compressed, and measured 0.9 × 0.1 cm at the coronal level of the nucleus accumbens. The septum pellucidum showed no fenestrations. The choroid plexuses were congested. The lamina terminalis and superior and inferior medullary vela were intact. The corpus callosum was not atrophic and was without hemorrhage or demyelination. The caudate nucleus, putamen, globus pallidus, thalamus, and subthalamic nucleus were normal, without lacunar infarcts or hemorrhages. The substantia nigra showed mild pallor. The internal capsule, basal nucleus of Meynert, amygdala, and piriform cortex were intact and without atrophy. The hippocampus and parahippocampal gyrus revealed no anomalies or gross atrophy. The mamillary bodies and hypothalamus were normal. The midbrain, pons, and medulla oblongata revealed no hemorrhages, infarcts, or demyelination. The pituitary gland was normal.

Sections from 23 brain areas were submitted for histological tissue processing and analysis, including the middle frontal gyrus, cingulate gyrus, anterior corpus callosum, caudate nucleus, insula cortex, putamen and globus pallidus, hippocampus at the level of the lateral geniculate body, thalamus, midbrain at the level of the red nucleus and the substantia nigra, pons at the level of the locus ceruleus, medulla at the level of the inferior olivary nucleus, cerebellum with dentate nucleus, basal nucleus of Meynert, amygdala, inferior parietal lobule, superior and middle temporal gyri, occipital lobecalcarine cortex, superior cerebellar vermis, splenium of corpus callosum, mamillary body and hypothalamus, pituitary gland, and dura mater. The following histochemical and immunohistochemical stains were performed on each section of the brain: hematoxylin and eosin, β-A4 amyloid immunostain, τ protein immunostain, neurofilament immunostain, α-synuclein immunostain, ubiquitin immunostain, amyloid precursor protein immunostain, and Bielschowsky silver impregnation stain. The section of the dura mater was stained only with hematoxylin and eosin.

Microscopic examination revealed sparse to moderate infiltration of the leptomeninges by neutrophils, accompanied by acute congestion of the leptomeningeal vessels, consistent with ethylene glycol-induced chemical leptomeningitis (16). There was mild neocortical neuronal dropout in the frontal, parietal, and temporal lobes, with residual normal laminar and columnar organization. Swollen, achromasic, or ballooned neurons were absent. There was mild extracellular edema of the cortical gray and white matter. Very focal and sparse perivascular oxalate microcrystals were noted. The centrum semiovale and the corpus callosum revealed no demyelination, pallor, or axonal spheroids. The ependymal lining showed intermittent denudations with focal infiltration of the occipital horn by neutrophils. There was patchy subependymal gliosis. The globus pallidus showed mild neuronal dropout. The internal, external, and extreme capsules and claustrum revealed no demyelination or degeneration.

The Sommer's sector, presubiculum and subiculum revealed cytoplasmic eosinophilia of many pyramidal neurons without neuronal dropout. The basal nucleus of Meynert and the amygdala revealed no neuronal dropout. The substantia nigra revealed mild neuronal dropout accompanied by mild extraneuronal pigment. The locus ceruleus also revealed mild neuronal dropout. The medulla oblongata revealed mild neuronal dropout and astrogliosis of the dorsal inferior olivary nucleus. There was mild neuronal dropout of the Purkinje neurons, without acute eosinophilic degeneration, as well as mild Bergmann astrogliosis. There was mild neuronal dropout of the internal granule cell layer and the dentate nucleus, which revealed mild fibrillary astrogliosis. The adenohypophysis revealed focal interstitial fibrosis with very focal sparse infiltration by

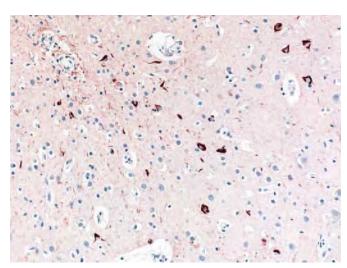


FIGURE 1. Photomicrograph ($\times 100$) of a section of the frontal neocortex immunostained for τ protein, showing frequent NFTs and NTs.

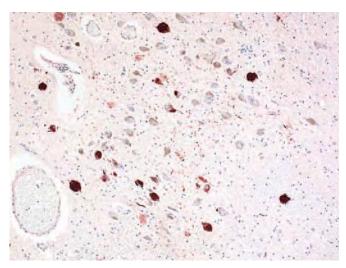


FIGURE 2. Photomicrograph ($\times 100$) of a section of the locus ceruleus immunostained for τ protein, showing frequent NFTs and NTs.

lymphocytes. The neurohypophysis was unremarkable. The dura mater was congested and revealed no inflammation or remote hemorrhage.

Immunohistochemical Findings

Diffuse or neuritic amyloid plaques and cerebral amyloid angiopathy were absent in all regions of the brain examined. τ-positive band- and flame-shaped small and large globose perikaryal NFT were topographically observed in several regions (*Figs. 1* and 2). The NFTs were also accompanied by τ-positive NTs. Large globose NFTs were found only in the midbrain, pons, basal nucleus of Meynert, substantia nigra, mammillary bodies, and hypothalamus. *Table 1* shows the dis-

TABLE 1. Summary of topographic distribution and density of neurofibrillary tangles and neuropil threads^a

Region of the brain	Density of NFTs	Density of NTs		
Frontal lobe, left	+++	++		
Cingulate gyrus, corpus callosum,				
and caudate nucleus, left				
Cingulate cortex	+	+		
Caudate nucleus	+*	+*		
Insular cortex, putamen and				
globus pallidus, left				
Insular cortex	++*	++*		
Putamen	+*	+*		
Globus pallidus	0	0		
Hippocampus, left				
CA-1, CA-2, CA-3	+	+		
Subiculum, presubiculum	+	+		
Entorhinal cortex	+++	+++		
Thalamus, left	+	+		
Midbrain, level of red nucleus				
Superior colliculi/oculomotor nucleus	+	+		
Substantia nigra	++*	++*		
Pons, level of locus ceruleus	1 1			
Locus ceruleus	+++	+++		
Other pontine tegmental nuclei	+	+		
Medulla	+	+		
Cerebellum	0	0		
Basal nucleus of Meynert	+	+		
	++	+		
Amygdala				
Inferior parietal lobule, left	++	+		
Superior and middle temporal gyri, left	+++	++		
Occipital lobe, calcarine cortex, left	0	0		
Superior cerebellar vermis	0	0		
Splenium of corpus callosum				
Posterior cingulate cortex	+	+*		
Corpus callosum	n/a	0		
Hippocampus, right				
Cornu ammonis (CA1–3)	++	++		
Subiculum	+	+		
Entorhinal cortex	++	++		
Mamillary body and hypothalamus, left	++	++		
Substantia nigra, cut left side	++	++		
Rostral pons/caudal midbrain				
Locus ceruleus	+++	+++		
Other tegmental nuclei	+	+		
Mid/caudal pons				
Locus ceruleus	+++	+++		
Other tegmental nuclei	+	+		

 $[^]a$ NFTs, neurofibrillary tangles; NTs, neuropil threads; +, sparse density; ++, moderate density; +++, frequent density; ++*, sparse-to-moderate density; +*, very sparse; n/a, not applicable.

tribution and density of NFTs and NTs in the regions of the brain examined. The determination of the density of NFTs and NTs was adapted from the density distribution of neuritic plaques by the Consortium to Establish a Registry for Alzheimer's Disease, which is used for the neuropathological diagnosis of Alzheimer's disease (9, 12, 23). One or two astrocytes in the subcortical white matter showed focal cytoplasmic fibrillary τ immunoreactivity. τ -positive tufted astrocytes, thorn astrocytes, and astrocytic plaques were absent in all regions of the brain examined. Lewy bodies, Lewy-related neurites, α -synuclein-positive glial inclusions, and neuronal or glial ubiquitin-positive inclusions were absent in all regions of the brain examined.

Acute toxic axonal injury and cerebral edema caused by acute ethylene glycol intoxication was evinced by multifocal axonal white matter immunoreactivity for amyloid precursor protein in the subcortical white matter and brainstem (15, 25).

APOE Genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA). Restriction fragment length polymorphism analysis with Hha I (New England Biolabs, Beverly, MA) was completed using previously published protocols (20, 27). The genotype of the sample was determined to be E3/E4 (*Fig. 3*).

DISCUSSION

Major depression, dementia-related syndromes, and neuropsychological and sensory motor deficits have been reported in professional and amateur contact sport players, including

NFL players (6, 8, 10, 17–19, 21, 22, 38, 46–49). The neuropathological findings responsible for these neuropsychiatric deficits have not been clearly defined because of the rarity of autopsies in retired NFL players.

Our case represents a retired professional player (who played a total of 14 vr of organized football) who had developed a progressive major depressive disorder after retirement from football, accompanied by repeated suicide attempts and a completed suicide by ingestion of ethylene glycol. Autopsy confirmed the presence of abnormal metabolism and widespread neuronal and neuropil accumulation of a cytoskeletal protein to form NFTs and



FIGURE 3. Polyacrylamide gel electrophoresis showing DNA stained with ethidium bromide visualized with ultraviolet light. Lanes 1 and 2 contain duplicate samples of the DNA extracted from the brain sample amplified as described in the text and digested with Hha to reveal the restriction fragment length polymorphism. Lane 3 is a sample known to be E2/E4 prepared in parallel with the samples from Lanes 1 and 2. Lane 4 is a negative template control. Lane 5 contains a 50 to 2000 basepair ladder.

NTs. The major components of NFTs and NTs are hyperphosphorylated paired helical filaments of the microtubule-binding protein, τ (16).

Abnormal metabolism and accumulation of neuronal cvtoskeleton and membrane proteins have been suggested to be pathoetiological components of delayed neurological sequelae of single or repeated MTBI sustained in contact sports (2, 13, 14, 41, 42). The morphophenotype of our case, i.e., the presence of NFTs without amyloid plaques, supports previous findings of Geddes et al. (13, 14) who found only NFTs in the brains of five young adults who had experienced

mild chronic head injuries. Geddes et al. (13, 14) had hypothesized that repetitive head injury in young adults may be initially associated with neocortical NFT formation in the absence of β -amyloid.

The APOE genotypes of our two reported cases were different (E3/E3 and E3/E4). We currently do not have any explanation for this difference. However, it confirms what is already known regarding APOE genotype (3, 11, 24, 25, 44). Individuals who inherit one or two copies of APOE4 may exhibit a three- to

TABLE 2. Common and contrasting features of two reported cases of chronic traumatic encephalopathy in two retired National Football League players^a

Characteristics	Patient 1	Patient 2	
Age at death	50 years	45 years	
Approximate age when decedent was drafted into the NFL	22 years	25 years	
Duration of professional play in the NFL	17 years	8 years	
Approximate duration of play of football in high school,			
college, and/ or in the military	5 years	6 years	
Interval between retirement from the NFL and death	12 years	12 years	
History and diagnosis of major depressive disorder after			
retirement from the NFL	Present	Present	
Gross atrophy of the brain and hydrocephalus ex vacuo	Absent	Absent	
Fenestrations of the septum pellucidum	Absent	Absent	
Cavum septi pellucidi	Absent	Present	
Presence of diffuse amyloid plaques	Present	Absent	
Presence of NFTs and NTs	Present	Present	
APOE genotype	E3/E3	E3/E4	
Postmortem diagnosis of coronary atherosclerotic disease	Present	Present	
Premortem history of steroid use	Present	Present	

^a NFL, National Football League; NFTs, neurofibrillary tangles; NTs, neuropil threads; APOE, apolipoprotein-E.

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ninefold increase in developing chronic posttraumatic neurodegeneration. However, the presence of the APOE4 allele does not confer absolute predisposition to CTE, and absence of APOE4 does not confer absolute protection from CTE.

Table 2 illustrates the common and contrasting features of our two reported cases of CTE in two NFL players. Both had long careers without multiple recorded concussions. Reasons for contrasting features in the two cases are not clear. There was a history of steroid use during play in the NFL in both cases. This observation may suggest that there is an unconfirmed possibility that steroid use may play a role in the pathoetiology of CTE. However, we cannot allude to this role of steroid use at this time. Further studies are needed to identify and define the pathoetiological factors and neuropathological cascades of CTE in retired football players.

The neuropsychiatric presentation and clinical course of CTE in football players and other contact-sport players including boxers (dementia pugilistica) may exhibit a spectrum of neuropsychiatric and neuropathological cascades. However, definitive characteristics of CTE in contact sports and American football should be determined by long-term, longitudinal, multi-institutional, and multidisciplinary studies, which will comprise genetic analysis and scheduled intermittent neuropsychiatric testing and follow-up, accompanied by neuroradiological monitoring of a specified cohort of professional contact-sport players, such as the players in the NFL Hall of Fame. Autopsies and comprehensive postmortem neuropathological examinations should be performed on all participants in these studies for brain tissue analysis and clinicopathological correlations.

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COMMENTS

This is an interesting study linking the chronic head trauma in professional football players with chronic traumatic encephalopathy. There is a temporal association of the symptoms with the patient's

football career. Also, it does not prove that head injury from playing football was the sole cause of this patient's disease; the association is intriguing and is important to report.

Kenneth Aldape Houston, Texas

The authors have had the opportunity to perform neuropathological studies on the brains of two National Football League (NFL) players with significant neuropathological differences in terms of the genotype, the presence (and absence) of amyloid plaques, and history. They concluded that a specific cohort of football players, such as those elected to the NFL Hall of Fame, should have autopsies and comprehensive postmortem neuropathological examinations regardless of premorbid conditions. The purpose would be to determine whether or not chronic neurodegenerative changes can be causally related to football participation.

From a scientific perspective, the goal certainly seems laudable. This case, however, exemplifies the difficulty in such a study. In their premortem history, the authors state that, "within several years of his retirement from the NFL, his [present] wife reported that he became increasingly quiet, he was noted to be afraid and fearful with paranoid tendencies." They also report that he became extremely reclusive and distanced himself from all personal interactions with family and friends. Because the authors did not speak with his first wife, or obtain history from the players, trainers, and others with whom he associated in an intensely competitive environment for more than 8 years, the statement that abnormal behavior began "within several years of his retirement from the NFL" could certainly be challenged.

Indeed, after an automobile accident after his third year in the NFL, the authors state that medical records from a local psychiatric hospital indicated that he had the diagnosis of "a major depressive disorder, severe, without psychotic features." In 1990, 2 years before his retirement, he was suspended by the NFL for steroid abuse. The duration for which he used steroids is unrecorded or unknown.

In 1991, 1 year before his retirement, he attempted suicide by the ingestion of rat poison and cold medications, and, as the authors state, there were several other subsequent suicide attempts by ingestion of prescription drugs and antifreeze. After another suicide attempt in 2003 and the conviction for arson in 2005, he subsequently died from ingestion of ethylene glycol.

With such a multifactorial and incomplete history, I think it is extremely speculative to suggest that his psychosocial behavior and neuropathological findings are attributable to football-induced traumatic encephalopathy, especially because he demonstrated no residual evidence of a post concussion syndrome after his one documented cerebral concussion, after which he returned to full football participation for several years. Nevertheless, although more than daunting, to perform postmortem neuropathological examinations on all NFL Hall of Fame inductees would be of interest.

Joseph C. Maroon *Pittsburgh, Pennsylvania*

Omalu et al. report the second case of a relatively young, retired NFL player whose autopsy showed widespread changes, which they speculate may have been related to episodes of mild traumatic brain injury (MTBI) during his many years of contact sport participation. Pathological brain findings included widespread accumulation of Ù-positive neurofibrillary tangles and neuropil threads, a cavum septum pellucidum, but no hippocampal or cerebellar atrophy. This athlete's medical history, having participated in organized football for

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14 years, had numerous episodes of behavorial abnormalities, along with a progressive major depressive disorder, multiple suicide attempts, and a completed suicide. However, there is no information concerning whether or not there were documented occurrences of clinical concussion related to football or if there were instances of MTBI at other stages of his life.

This report follows upon the authors' initial study of a similarly aged, football experienced, and psychologically disturbed retired NFL player whose autopsy findings showed both similar and contrasting features. Differences in this second case, although unclear if pertinent, were absence of amyloid plaques, an E3/E4 genotype, and diffuse topographic distribution of sparse to frequent neurofibrillary tangles and neuropil threads in not only the neocortex, but also the hippocampus, subcortical ganglia, and brainstem.

We now appreciate that, after sports concussion, a transient hypermetabolic state, axonal injury, a lower threshold for recurrence, and cumulative effects may occur (2, 6, 8). The old standard of a negative neurological examination and computed tomographic study to exclude central nervous system damage is no longer valid. Newer evaluations, focusing on white matter injury, hold promise to detect the presence of injury (1). Also, as McKeag has recently pointed out, there has been a previous tendency to overgeneralize in our approach to athletic MTBI and in studying its effects, as a wide range of variability in the type and expression of injury to the human brain is to be expected (7). Our previous study of former NFL players suggested that there was a correlation between the exposure to athletic MTBI and mild cognitive impairment seen in the later years after retirement (5).

Following on their initial case report, this autopsy study is of interest and further raises the question of the possibility of chronic or cumulative effects of multiple, subclinical concussions resulting in neurodegenerative changes in the form of accumulation of neuronal cytoskeleton and membrane proteins. Notwithstanding the absence of documentation of multiple clinical concussive episodes, this case nonetheless stimulates the discussion of whether or not, in a small number of players, such football exposure can cause a widespread neurodegenerative process with ultimate clinical manifestations.

It is uncertain whether or not these two case reports, unprecedented for such athletes, represent random findings or if there is a posttraumatic state which is akin to, but dissimilar enough not to satisfy all the classic neuropathological findings of, dementia pugilistica (3, 4). It remains an important, but unanswered question, which will have to be addressed by future necropsy and longitudinal population studies of athletes' exposure to known MTBI and subclinical concussions and their subsequent clinical and neurocognitive outcomes in the years after retirement.

Julian E. Bailes Morgantown, West Virginia

- Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, Jordan BD: Association between recurrent concussion and late-life cognitive impairment in retired professional football players. Neurosurgery 57:719–726, 2005.
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This article adds to the increasing literature regarding cognitive deficits associated with low-grade repetitive head injury. Although, as a case report, no definitive statements can be made, it is important to have such cases presented and discussed. Although it is not possible to exclude a coincidental association of a psychiatric disorder in a professional NFL player, the degenerative pathology described would certainly be more in keeping with a traumatic etiology. Clearly, cases such as this provide an opportunity for more detailed studies looking at potential mechanisms underlying cognitive decline in chronic repetitive head injury, such as neuroinflammatory mechanisms. The genetic information relating to apolipoprotein E is of limited interest as a number of one (or two, when the previous report is included) is not informative.

Colin Smith Neuropathologist Edinburgh, Scotland

The authors present a case of autopsy-confirmed chronic traumatic encephalopathy in a retired professional football player with a history of neuropathological features. He had a 14-year history of involvement in organized football without multiple recorded concussions. After retirement, he was diagnosed with severe major depressive disorder and committed suicide 12 years after retirement. The contribution of anticoagulant rodenticide and ethylene glycol ingestion to his demise is unclear. The patient underwent an autopsy with restriction fragment length polymorphism analysis performed to determine apolipoprotein E genotype. His apolipoprotein E genotype was E3/E4, which would suggest, though not with certainty, a three- to ninefold increase in developing chronic posttraumatic neurodegeneration. Neurofibrillary tangles and neuropil threads were noted on evaluation of the cerebrum.

The authors compare and contrast this case with a previous case report. The relationship of the onset of his depressive disorder after his history of participation in football is purely temporal. This is a difficult relationship, given a potential history of antisocial behavior before his retirement. It becomes additionally more complex given a history of steroid use.

This report will hopefully bear subsequent studies, as the authors appropriately suggest, which will require long-term, longitudinal, multi-institutional and multi-disciplinary evaluation of genetic disposition, neuropsychiatric history, neuroradiological findings, clinical follow-up, and comprehensive postmortem neuropathological examinations.

Min Park Andy Nguyen Michael L. Levy San Diego, California

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EXHIBIT 58

http://www.cnn.com/2013/08/30/us/nfl-concussions-fast-facts/

Cases 48-2012md-Document: 000311138165801-1Pageile5870/06Date Pitege: 08/0972019 NFL Concussions Fast Facts

By CNN Library updated 1:29 PM EDT, Mon July 21, 2014

CNN.com

(CNN) -- Here's some background information about concussions in the NFL. Reports show an increasing number of retired NFL players who have suffered concussions developed memory and cognitive issues such as dementia, Alzheimer's, depression and chronic traumatic encephalopathy (CTE).

A concussion is a type of traumatic brain injury caused by a blow to the head.

Facts:

Most concussions occur without losing consciousness.

Chronic traumatic encephalopathy (CTE) is a degenerative disease of the brain and is associated with repeated head traumas like concussions.

Among the plaintiffs in concussion-related lawsuits: Art Monk, Tony Dorsett, Jim McMahon, Jamal Anderson and Ray Easterling.

Common Symptoms of Concussions: (The NFL Player Concussion Pamphlet)

Imbalance

Headache

Confusion

Memory loss

Loss of consciousness

Vision change

Hearing change

Mood change

Fatigue

Malaise

Statistics: (NFL)

2012 - 261 diagnosed concussions during preseason and regular-season practices and games combined.

2013 - 228 diagnosed concussions during preseason and regular-season practices and games combined.

Timeline:

1994 - NFL Commissioner Paul Tagliabue creates the Mild Traumatic Brain Injury Committee. Dr. Elliot Pellman is named chairman despite not having experience with brain injuries.

2002 - Dr. Bennet Omalu, a forensic pathologist and co-founder of the Brain Injury Research Institute, identifies chronic traumatic encephalopathy (CTE) in the brain of former Pittsburgh Steelers' center Mike Webster, 50, who committed suicide. Omalu is the first to identify CTE in American football players.

January 2005 - The NFL's Mild Traumatic Brain Injury Committee finds that returning to play after sustaining a concussion "does not involve significant risk of a second injury either in the same game or during the season."

2005 and 2006 - Dr. Omalu identifies chronic traumatic encephalopathy (CTE) in the brains of former Pittsburgh Steelers players Terry Long, 45, and Andres Waters, 44. Both had committed suicide.

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February 2007 - Dr. Elliot Pellman steps down as chairman of the Mild Traumatic Brain Injury Committee but remains on the committee.

June 2007 - The NFL holds a medical conference on concussions.

August 14, 2007 - The NFL formalizes new concussion guidelines which include a telephone hotline to report when a player is being forced to play contrary to medical advice.

October 28, 2009 - Part I of the House Judiciary Committee hearing on Legal Issues Relating to Football Head Injuries. NFL Commissioner Roger Goodell defends the League's policy regarding concussions.

January 4, 2010 - Part II of the House Judiciary Committee hearing on Legal Issues Relating to Football Head Injuries. Dr. Ira Casson, one of the co-chairs of the Mild Traumatic Brain Injury Committee, denies a link between repeat head impacts and long-term brain damage.

March 2010 - The NFL's Mild Traumatic Brain Injury Committee is renamed the Head, Neck and Spine Committee. Two new co-chairs are selected, and Dr. Elliot Pellman is no longer a member of the panel.

October 20, 2010 - NFL Commissioner Goodell issues a memo to all 32 teams that warns of possible suspensions for offenders that violate the "playing rules that unreasonably put the safety of another player in jeopardy have no place in the game, and that is especially true in the case of hits to the head and neck."

February 17, 2011 - Former Chicago Bears defensive back Dave Duerson, 50, commits suicide with a gunshot wound to the chest rather than his head so his brain can be researched for chronic traumatic encephalopathy (CTE). Boston University researchers find CTE in Duerson's brain, the same disease found in other deceased NFL players.

April 19, 2012 - Former Atlanta Falcons safety Ray Easterling, 62, commits suicide. An autopsy finds signs of chronic traumatic encephalopathy (CTE). Easterling had been a plaintiff in a class action lawsuit against the NFL over concussion-related injuries filed in August 2011.

May 2, 2012 - Former NFL linebacker Junior Seau, 43, is found dead with a gunshot wound to the chest, classified as a suicide. Friends and family members say the suicide was brought on by multiple concussions, but an initial autopsy report finds no apparent brain damage. Portions of Seau's brain have been sent to the National Institutes of Health for further study.

June 7, 2012 - A unified lawsuit combining more than 80 concussion-related lawsuits on behalf of more than 2,000 National Football League players is filed in federal court in Philadelphia. The players accuse the NFL of negligence and failing to notify players of the link between concussions and brain injuries, in Multi-district Litigation Case No. 2323.

August 30, 2012 - The NFL files a motion to dismiss the concussion-related lawsuits filed by former players.

September 5, 2012 - The Foundation for the National Institutes of Health announces that the NFL has committed to donating \$30 million to support research on medical conditions prominent in athletes.

January 10, 2013 - The National Institutes of Health releases the results of their analysis of Junior Seau's brain tissue confirming that Seau did suffer from chronic traumatic encephalopathy (CTE).

January 23, 2018 2017 Control of a brain disease caused by violent hits he endured while playing the game.

August 29, 2013 - The NFL and ex-players reach a deal in the class action lawsuit that calls for the NFL to pay \$765 million to fund medical exams, concussion-related compensation, medical research for retired NFL players and their families, and litigation expenses, according to a court document filed in U.S. District Court in Philadelphia. The agreement still needs to be approved by the judge assigned to the case, which has grown to include more than 4,500 plaintiffs.

December 13, 2013 - The body of former NFL linebacker Jovan Belcher is exhumed in order to perform tests on his brain, a lawyer for the player's family tells the Kansas City Star. On December 1, 2012, Belcher, 25, shot his longtime girlfriend to death and then killed himself.

December 2013 - Ryan Freel is the first Major League Baseball player to be diagnosed with chronic traumatic encephalopathy (CTE), according to researchers at the Boston University School of Medicine. Freel committed suicide in December 2012 at the age of 36.

January 14, 2014 - A federal judge declines to approve a proposed \$760 million settlement of claims arising from concussions suffered by NFL players, saying she didn't think it was enough money.

May 28, 2014 - Former Miami Dolphins quarterback Dan Marino, and 14 other former NFL players, sues the NFL over concussions. The lawsuit claims the NFL knew for years of the link between concussions and long-term health problems.

June 3, 2014 - It is reported that Dan Marino has withdrawn his name from the concussion lawsuit.

July 17, 2014 - Former NFL players Christian Ballard and Gregory Westbrooks file suit against the NFL Players Association, alleging the union withheld information about head injuries.

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EXHIBIT 59

Neurosurg Focus 21 (4):E12, 2006

Concussion in professional football

Summary of the research conducted by the National Football League's Committee on Mild Traumatic Brain Injury

ELLIOT J. PELLMAN, M.D., AND DAVID C. VIANO, DR. MED., PH.D.

Mild Traumatic Brain Injury Committee, National Football League, New York, New York; ProHEALTH Care Associates, Lake Success, New York; and ProBiomechanics, Bloomfield Hills, Michigan

√In 1994 the National Football League (NFL) initiated a comprehensive clinical and biomechanical research study of mild traumatic brain injury (TBI), a study that is ongoing. Data on mild TBIs sustained between 1996 and 2001 were collected and submitted by NFL team physicians and athletic trainers, and these data were analyzed by the NFL's Committee on Mild Traumatic Brain Injury. At the same time, analysis of game videos was performed for on-field mild TBIs to quantify the biomechanics involved and to develop means to improve the understanding of these injuries so that manufacturers could systematically improve and update their head protective equipment. The findings and analysis of the Committee have been presented in a series of articles in *Neurosurgery*.

KEY WORDS • traumatic brain injury • sports-related concussion • neuropsychological assessment

N 1992 Al Toon, who was a wide receiver for the New York Jets, was the first NFL player known to have retired because of postconcussion syndrome.² The year after Mr. Toon's retirement, another player, Merrill Hoge of the Chicago Bears, retired because of the same problem. Commissioner Paul Tagliabue, team physicians, and many others raised questions: was this a new problem or a misdiagnosed or unrecognized one? Was this a statistical anomaly or the beginning of an epidemic?

It was decided that a rigorous, scientific approach was necessary to gather the data to answer these questions for this high-profile professional sports league. In 1994, Commissioner Tagliabue approved the creation of the NFL's Committee on Mild Traumatic Brain Injury. 12 The Committee was composed of experts inside and outside the NFL. It was decided by the Committee that protection against injury as well as collection and analysis of injury data would be critical to the success of their mission. For the study, a reportable mild TBI was defined as a traumatically induced alteration in brain function manifested by an alteration of awareness and consciousness, including but not limited to an LOC, a "ding," a sensation of being dazed or stunned, a sensation of "wooziness" or "fogginess," a seizure or amnesic period, and by symptoms commonly associated with postconcussion syndrome, including persistent headaches, vertigo, lightheadedness, loss of balance, unsteadiness,

Abbreviations used in this paper: CI = confidence interval; ImPACT = Immediate Postconcussion Assessment and Cognitive Testing; LOC = loss of consciousness; mph = miles per hour; NFL = National Football League; NOCSAE = National Operating Committee on Standards for Athletic Equipment; SI = severity index; TBI = traumatic brain injury.

syncope, near-syncope, cognitive dysfunction, memory disturbances, hearing loss, tinnitus, blurred vision, diplopia, visual loss, personality change, drowsiness, lethargy, fatigue, and inability to perform usual daily activities. ¹⁰ The research summarized here was developed, supervised, and completed in response to the stated goals of the NFL's Committee on Mild Traumatic Brain Injury.

Protection Against Mild TBI

I: Helmet Standards

Next to impact avoidance, football helmets are the most important factor in protecting a player from mild TBI. In 1973, the NOCSAE established standards for the impact performance of football helmets. The NOCSAE standard limited the SI, which is based on resultant head acceleration. All new football helmets available for use in high school and college football were then certified to the NOCSAE standard, and the wearing of such helmets was made mandatory for college players in 1978 and for high school players in 1980.

The certified helmets cut the SI score by half compared with the headgear worn before the establishment of the standard. By 1980, significant reductions in injuries were observed after the voluntary adoption of the standards by helmet manufacturers. The injury reduction was believed to be the result of the helmet design changes, which targeted serious brain injuries such as brain contusion. Despite the improvement of helmet design for the prevention of serious brain injury, little was known regarding the effectiveness of football helmets in protecting against mild TBI at the time of the initial research conducted by

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the NFL's Committee on Mild Traumatic Brain Injury. Therefore, the Committee planned a series of research projects aimed at defining the biomechanics of concussive impacts in professional football.

After consideration of various alternatives, the effort focused on analyses of game videos of plays that had resulted in concussions. Experts in biomechanics proposed that, with multiple views of the impact and line markings on the field, the direction and speed of concussive impacts could be determined. Cinematographic analysis methods were developed to determine the actual speed at which players were moving before colliding (Fig. 1). This would allow laboratory reconstructions (reenactments) of the game impacts by using instrumented test dummies to simulate the helmeted players. The reenactments closely matched the situations on the field.

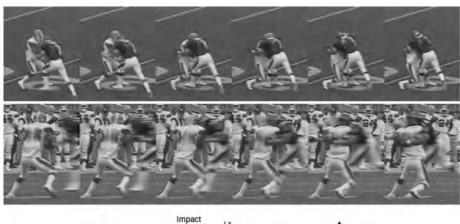
Reconstruction of the game impacts involved two Hybrid III anthropometric test devices. Two high-speed videos recorded head kinematics in the reconstruction. The cameras were positioned identically to the views from the game video to allow one-to-one comparison (Fig. 2). With the aid of transducers placed in the head of the dummy, the translational and rotational accelerations of the head could be determined in concussive and noninjurious impacts. Matching the available on-field injury video to clinically confirmed mild TBI made determination of an appropriate "event" possible and verifiable. All mild TBI events in the players were examined, confirmed, and recorded by NFL team physicians.

When a mild TBI occurred on the field, it was evaluat-

ed by a physician and athletic trainer, who completed forms describing the impact and the injury. Mild TBIs were also reported to a biomechanical engineering group contracted to analyze and reconstruct game impacts. Television network tapes of games were obtained from the NFL and analyzed.

The most striking observation in this study is that concussion in professional football involves a mean impact velocity of 9.3 m/second (20.8 mph) and a head velocity change of 7.2 m/second (16.1 mph). These are exceptionally high velocities and accelerations and long durations. Automotive crashes typically involve impact durations of less than 6 msec for head impacts with vehicle rails, pillars, and structures. The NFL results established new information on tolerances in the 15-msec range; there had been a virtual absence of scientific data on human tolerance. The NFL reconstruction data also supported a value of 70 to 75 G for concussion in padded impacts, which is at the high end of earlier tolerance ranges but is consistent with the Wayne State University concussion tolerance curve. Most important, the initial study demonstrated the strong correlation of concussion with translational acceleration, which should therefore be the primary measure for assessment of the performance of helmet protection systems.10

One conclusion of the initial biomechanical study was that the current NOCSAE SI and the more widely accepted Head Injury Criterion are adequate performance measures for helmet standards and that the added complexity of measuring rotational acceleration may not be needed



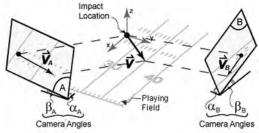


Fig. 1. Still photographs from films showing game action and mathematical calculations of the vector of impacts. The impact velocity of game hits was determined by analysis of two camera views of the collision. *Upper:* The photos show the impact sequence from two views. *Lower:* Graph showing the camera locations and the perspective of the two video images of the game impact. The two perspectives are mathematically merged as vectors that change with each time-step of the video. (Reprinted in modified form with permission from Pellman EJ, Viano DC, Tucker AM, Casson IR, Waeckerle JF: Concussion in professional football: reconstruction of game impacts and injuries. **Neurosurgery 53:** 799–814, 2003.)

Concussion in professional football

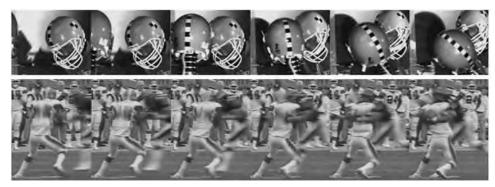


FIG. 2. Comparison of the laboratory reconstruction (*upper*) and still photos of the game impact (*lower*) from a case of concussion sustained in an NFL game. Refinements in the test setup were done until the helmet kinematics matched the game impact sequence. (Reprinted in modified form with permission from Pellman EJ, Viano DC, Tucker AM, Casson IR, Waeckerle JF: Concussion in professional football: reconstruction of game impacts and injuries. **Neurosurgery 53:** 799–814, 2003.)

for an improved or supplemental NOCSAE helmet standard. The results of this study provided a basis for new helmet evaluation methods, new helmet designs, and the prevention of concussions in football.

II: Biomechanical Testing

It was recognized by the Committee that a greater understanding of the location and direction of helmet impacts was needed to give manufacturers the ability to develop newer, improved mild TBI—resistant helmets. Therefore, NFL game videos were further analyzed for the typical locations of severe helmet impacts in professional football. The magnitude and direction of force causing concussion were determined by the use of selected cases that were reconstructed in laboratory tests.

A request was made to have a biomechanical testing contractor reconstruct the impact in 31 cases by using at least two clear video reviews of the collision. Laboratory

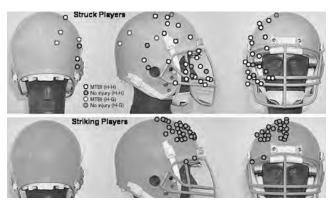


Fig. 3. *Upper:* Photographs of dummy heads showing location of initial helmet contacts for the struck players. Both concussive and nonconcussive impacts and falls to the ground are shown. *Lower:* The impact location for the striking players involved no concussions. The impact locations are all shown on the right side of the helmet, although the game impacts occurred on both sides. H-G = helmet-to-ground impact; H-H = helmet-to-helmet impact; MTBI = mild TBI. (Reprinted with permission from Viano DC, Pellman EJ: Concussion in professional football: biomechanics of the striking player—part 8. **Neurosurgery 56:** 266–280, 2005.)

tests would then be set up to reenact the game impacts with crash dummies and to measure head responses. The reconstruction emphasized helmet-to-helmet and helmet-to-ground impacts, because the video of other impacts was more obscured from clear view. Helmet contact of the struck player was categorized by the impact quadrant and head level for helmet contacts.

The study demonstrated the importance of face-mask injuries at an oblique angle, with the majority of contacts occurring below the head's center of gravity. Another important aspect was that it described the quadrants on the helmet for which future NOCSAE standards may establish performance requirements (Fig. 3). By defining relevant quadrants, greater performance may be ensured over a segment of the helmet in which risks of concussion are higher in professional football, particularly low on the side and back and oblique to the face mask.

The laboratory reconstruction of game impacts provided the Committee with data identifying the location and direction of helmet impacts associated with concussion in NFL players. It also provided unique biomechanical data on head responses associated with concussion. The response data also allowed the determination of injury risk functions for concussion.

Using the Logist function, the probability of concussion p(x) was related to various biomechanical parameters (x) measured in the reenactment tests by using the following formula: $p(x) = [1 + exp(\alpha - \beta x)]^{-1}$ where α and β are parameters fit to the NFL data. The parameters determined for NFL concussion were as follows: $\alpha = 2.677$ and $\beta = 0.0111$ for the Head Injury Criterion; $\alpha = 4.678$ and $\beta = 0.0573$ for translational acceleration; and $\alpha = 5.231$ and $\beta = 0.000915$ for rotational acceleration.

III: Head-Down Tackling

For decades head-down tackling (or so-called spearing) has been a concern because it can result in catastrophic neck injuries in the striking player. The epidemiological and cinematographic analyses of neck injuries have shown that axial loading with flexion or extension causes the majority of cervical fracture–dislocations. This evidence has resulted in rules changes in high school, college, and professional football banning deliberate spearing

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and the use of the top of the helmet as an initial point of contact in a tackle. It was observed that players who suffered concussions were sometimes struck by players who were using head-down tackling techniques. The Committee decided to study the biomechanics of this form of injury both in the striking player ("nonconcussed") and the player who was struck ("concussed").

Once again, game film and video were collected from the NFL and correlated with clinical mild TBI data supplied by each club's team physicians. Laboratory reconstruction was performed using Hybrid III male dummies. In the dummy representing the striking player, a six-axis neck transducer was installed between the head and the top of the neck.

In helmet-to-helmet impacts, the striking player lowers the head, neck, and torso to deliver maximum force to the struck player, whose head and neck resist the impact.¹⁵ This is the typical situation when the struck player does not see the tackle and does not prepare for the collision. The key to the concussive blow is the head-down position, which involves a 67% greater mass of the striking player by engaging his torso in the collision. Neck forces couple torso mass into the collision, which contributes to the higher effective mass of the striking player.

The prevention of concussion in the struck player provides another reason, besides preventing neck injuries in the striking one, to enforce rules against head-down tackling or spearing in football. Another means to lower concussion severity may be to reduce the stiffness of the top-crown portion of the helmet and to lower the mass of the helmet, although these changes may be less effective than enforcement of antispearing rules.

IV: Boxing

Because boxing entails considerable risk of closed head trauma, comparisons are often made between this sport and football regarding mechanisms of injury. The risk of concussion is considerably greater in professional boxing compared with professional football. The clinical picture of more severe brain injury is different in football and boxing. Boxers are much more likely to suffer subdural hematomas and deaths from brain injury than are professional football players. A better understanding of the biomechanics of head responses and mechanisms of brain injury would continue to lay the foundation for better protective headgear for sports.

Eleven Olympic boxers were included in this study.¹³ These athletes were instructed to strike an instrumented Hybrid III head with their gloved fist two times with four different punches (to the forehead and jaw and with a hook and an uppercut). The height and weight of each boxer were measured and anthropometric data for the dominant hand were collected to allow the effective hand–arm mass to be calculated. Instrumentation was placed in the boxer's clenched hand as well as in the Hybrid III head. A camera recorded the event at a lens speed of 4500 images per second. The punch and head inertial forces were measured.

There were three significant differences noted between the biomechanical forces exerted on the head and brain by boxing punches and the football helmet impacts in the NFL. The boxer's punches resulted in lower translational accelerations in the struck head compared with the football impacts (Fig. 4). The boxer's punch applied a higher moment to the struck head than did the football impacts. This resulted in a higher rotational acceleration in the head that was struck than did the football impacts. Boxers sustain a brain injury by two mechanisms: translational and rotational accelerations of the brain, with a preponderance of the rotational component. Professional football players, on the other hand, sustain mild TBI mostly by translational forces because the shell of the helmet allows the players to slide relative to one another, limiting head rotational accelerations. These differences were further studied using finite element analysis of brain responses.14 The localized strains in the brain and different biomechanical inputs help explain the clinical differences between head injuries in boxing and professional football.

Finite element modeling also showed that strains develop late, after the primary impact force, and focus on their response at the midbrain. This study shows a complicated interaction of the head kinematics, detailed geometrical and material properties of the brain, and the role of brain movement and deformation within the skull (Fig. 5).

V: Impact Velocity

In our earlier studies, we found that concussions in NFL players occur at an impact velocity of 9.3 ± 1.9 m/second (20.8 ± 4.2 mph) oblique on the face mask, side, and back of the helmet. There is a need for new testing methods to evaluate helmet performance in protecting against impacts causing concussion.

The NOCSAE certifies the helmets used by professional football players. The impact tests provide confidence that protective helmets are effective in reducing life-threatening head injuries. Data collected from the accelerometers used in the NOCSAE head drop test are used to assess the shock-attenuating properties of the helmet based on the head SI, in which the risk of serious head injury is

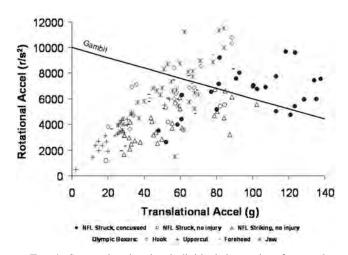


Fig. 4. Scatterplot showing individual data points for translational and rotational acceleration (Accel) of the Hybrid III head for NFL game impacts and four different Olympic boxing punches. (Reprinted with permission from Viano DC, Casson IR, Pellman EJ, Bir CA, Zhang L, Sherman DC, et al: Concussion in professional football: comparison with boxing head impacts—Part 10. **Neurosurgery 57:** 1154–1172, 2005.)

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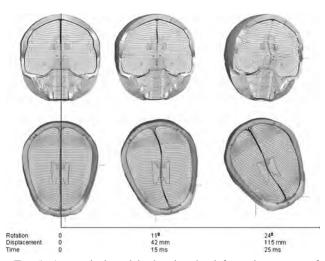


Fig. 5. Anatomical models showing the deformation pattern of the finite element brain from a frontal and superior view of the hemispheres at 0, 15, and 25 msec for one of the NFL concussion cases. The sequence shows the head kinematics and brain deformations. (Reprinted in modified form with permission from Viano DC, Casson IR, Pellman EJ, Zhang L, King AI, Yang KH: Concussion in professional football: brain responses by finite element analysis—part 9. **Neurosurgery 57:** 891–916, 2005.)

determined from the SI. This standard does not address helmet performance in reducing the risk of concussion.

It was believed by the members of the committee that the previous NFL mild TBI research findings would allow a recommendation to be made for a new methodology for testing helmets to reduce the risk of concussions. 11 The initial approach involved pendulum impactors that were used to simulate 7.4 and 9.3 m/second impacts causing concussion in NFL players. A helmet was placed on an instrumented Hybrid III head that was supported on the neck, which was fixed to a sliding table for frontal and lateral impacts. The testing evolved to a linear pneumatic impactor, which gives better control and a broader speed range for helmet testing. The NOCSAE has prepared a draft supplemental helmet standard for the 7.4- and 9.3m/second impacts evaluated using the new impactor. The proposed NOCSAE standard is the first to address helmet performance in reducing the risk of concussion.

VI: Performance of the Newer Helmets

The new understanding of the biomechanics of concussion in NFL players has enabled football helmet manufacturers to make design changes, for the first time, specifically to reduce the risk of mild TBI. The NFL testing techniques addressing concussion were shared previously with the helmet manufacturers and NOCSAE. The Adams USA Pro Elite, Riddell Revolution, and Schutt Sport Air Varsity Commander and DNA helmets are examples of headgear designed using the new information. Using the new mild TBI testing methodology, the Committee believed it would be useful to test the performance of newer helmets in reconstructed game impacts to compare them with a more standard VSR-4 football helmet.

The aim of this most recent study¹⁶ was to investigate the performance of newer football helmets under conditions causing concussion in NFL players. Ten cases of NFL

game concussions were selected for reenactment testing with newer helmets to investigate the equipment's effectiveness in reducing the risk of concussion. The range of impact speed was between 7.4 and 11.2 m/second for eight cases of helmet-to-helmet impacts. This was within one standard deviation of the average condition for concussion in the NFL. The two head-to-ground impact cases averaged 7.2 m/second. For each case of helmet-to-helmet impact, the striking and struck dummies were oriented to match the original laboratory reconstructions of NFL players' concussions. Verification tests ensured that the 10 reconstructed impacts from NFL games were set up similarly to the original testing. Identification on all helmets was obscured, and random tests were conducted.

Testing revealed that newer football helmets reduce concussion risks in collisions that were representative of NFL player experiences. Depending on the biomechanical response, the reductions are in the range of a 10 to 20% lower risk of concussion. The newer headgear reduces concussion risk by using thicker and more energy-absorbing padding on the side and back of the helmets and around the ears. This demonstrates an encouraging trend with the newer headgear; and we expect additional progress. The tests should help NOCSAE in its effort to finalize new helmet standards for preventing concussions.

Injury Collection and Data Analysis

I: Prevalence of Mild TBI

Mild TBI is a major public health problem in the US, with an estimated annual incidence of 160 to 375 cases per 100,000 persons per year. Officials at the Centers for Disease Control and Prevention have estimated that the number of mild TBIs has reached 300,000 cases per year in all sports. In an attempt to better understand mild TBI in the NFL, the Committee supervised prospective collection of data on this condition in NFL players from 1996 to 2001.

All data were collected using standardized forms, and the information was assessed in a blinded fashion. In all, 787 game-related cases (1913 games) were reported, and all players were examined by team physicians, with information reported on player position, type of helmet, symptoms, medical actions, and playing days lost.⁵ All patients were evaluated by physicians immediately after the injury and underwent follow-up physician evaluations until they returned to play. Forms were completed by the physicians, which increased the medical validity and reliability of the information collected. Because the Committee did not mandate case management for mild TBI, the patients' medical course reflects the true natural history of mild TBIs among professional football players during this 6-year period.

Mild TBIs are relatively common injuries sustained by professional football players. The data indicate that quarterbacks, wide receivers, defensive backs, and specialteam players on kicking units are more likely to sustain these injuries than are offensive and defensive linemen (Table 1). The clinical information helped validate the biomechanical data on professional football—related mild TBIs derived from the earlier studies.

The most common initial symptoms for players who sustained concussions were headaches, dizziness, memory

TABLE 1
Incidence of mild traumatic brain injury according to player position in National Football League games

-						
Position	No. of Cases	Incidence(%)	No. of Game Positions	Risk per 100 game-positions		
High Risk						
Offensive						
Quarterback	62	7.9%	3,826	1.62(1.22, 2.02)		
Wide Receiver	94	11.9%	7,652	1.23(0.98, 1.48)		
Tight End	36	4.6%	3,826	0.94(0.63, 1.25)		
Running Back	69	8.8%	7,652	0.90(0.69, 1.11)		
Defensive						
Secondary	143	18.2%	15,304	0.93(0.78, 1.08)		
Moderate Risk						
Offensive						
Offensive Line	56	7.1%	19,130	0.29(0.21, 0.37)		
Defensive						
Linebacker	52	6.6%	11,478	0.45(0.33, 0.57)		
Defensive Line	67	8.5%	15,304	0.44(0.34, 0.54)		
Special Team						
Return Ball Carrier	22	2.8%	3,826	0.58(0.34, 0.82)		
Kick Unit	131	16.6%	38,260	0.34(0.28, 0.40)		
Low Risk						
Special Team						
Punter	7	0.9%	3,826	0.18(0.05, 0.31)		
Return Unit	33	4.2%	38,260	0.09(0.06, 0.12)		
Kicker, FGA	1	0.1%	3,826	0.03(-0.02, 0.08)		
Kicker, PAT	1	0.1%	3,826	0.03(-0.02, 0.08)		
Holder	1	0.1%	3,826	0.03(-0.02, 0.08)		
Unknown/Undesignated	12	1.5%				
Total	787	100%		8.08		

^aRisk per 100 game-positions is the number of concussions divided by the number of times the position was played during the observed period of 3,826 games, multiplied by 100. Values in parentheses are 95% confidence intervals. FGA = field goal attempt; PAT = point after touchdown. Risk strata are approximate, because there is some overlap of confidence intervals.

(Table reproduced with permission from Pellman EJ, Powell JW, Viano DC, Casson IR, Tucker AM, Feuer H, et al: Concussion in professional football: epidemiological features of game injuries and review of the literature—part 3. Neurosurgery 54:81–96, 2004.)

problems, cognitive problems, and somatic complaints. Headaches were observed in 55% (95% CI 51.5–58.5%) of NFL players who suffered concussions.⁵ For the great majority of these players, mild TBIs did not cause prolonged disability or prolonged absence from play. In the NFL, 56.5% of players with concussions returned to play on the day of the injury and 97.1% returned to play by Day 9 after the injury. Only 2.9% of the players missed more than 9 days before returning to play. This indicates that most mild TBIs sustained in the NFL are self-limiting and that players recover fully and spontaneously in a short time. Because a significant percentage of players returned to play in the same game and the overwhelming majority of players with concussions were kept out of football-related activities for less than 1 week, it can be concluded that mild TBIs in professional football are not serious injuries.

Only 9.3% (95% CI 7–11.6%) of the NFL players experienced an LOC as a result of severe concussive head impacts (58 of 623 reported cases of mild TBI). It is important for all physicians who care for athletes with head injuries to know that most of the concussions they treat are not associated with LOC, and that when this symptom occurs it is for a relatively short duration.

II: Repeated Mild TBI

Despite the findings and conclusions in the preliminary clinical study, questions remained concerning NFL players who suffered repeated mild TBIs. Physicians have been concerned for many years about the possible deleterious effects of multiple concussions on the brains of athletes. In this study, data on 887 concussions sustained in practices and games involving 650 players from all 30 NFL teams between 1996 and 2001 were prospectively collected and analyzed. A total of 160 players experienced repeated injury, with 51 suffering three or more concussions during the study period. The median time between injuries was 374.5 days, with only six concussions occurring within 2 weeks of the initial injury. Repeated concussions were more prevalent in the secondary, the kick unit on special teams, and in wide receivers.

There have been reports in which researchers have concluded that there may be an increased risk of repeated concussive injuries, and there may be a slower recovery of neurological function after repeated concussions in those who have a history of previous ones. The results of this study in professional football players do not support that conclusion. Although approximately one half of players returned to play during the same game or practice session, and approximately 90% returned within 1 week, recurrent injury caused by an increased vulnerability in the immediate postconcussion period does not seem to be a factor in professional football players.

No cases of "second-impact syndrome" were detected during the 6-year period of this NFL study. There were no deaths, prolonged comas, or evidence of diffuse cerebral

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edema in any player. Furthermore, there have been no case reports of second-impact syndrome in the history of the NFL. It is possible that this syndrome does not truly exist in this population of athletes. Many of the mild TBI guidelines have established exclusion periods based at least partially on the belief that everyone who experiences a symptomatic mild TBI is at risk for the development of second-impact syndrome. The absence of the syndrome in this patient population supports the suggestion that such arbitrary return-to-play guidelines may be too conservative for professional football.

Another often-expressed concern underlying the development of mild TBI guidelines is the occurrence of chronic brain damage as a result of multiple head injuries. A recent letter to the editor in *Neurosurgery* addressed the case of an NFL player who was alleged to have died of complications of chronic traumatic encephalopathy, underscoring this concern.¹ Chronic traumatic encephalopathy in boxers is a well-accepted and documented clinical and pathological syndrome. The clinical features include a combination of cerebellar, extrapyramidal, and pyramidal dysfunction, along with cognitive and personality changes. In the NFL study, none of these features was identified in any player, including those with repeated injury. There were no signs of chronic traumatic encephalopathy in this group of active, contemporary football players.

In players with four or more concussions there was a greater chance of personality change and fatigue, but the number did not reach statistical significance. The incidence of LOC at the time of mild TBI was no different with successive concussions. Overall, however, the signs and symptoms reported in the NFL study were very similar in players with single and multiple mild TBIs. There was no evidence of increased severity of injury in multiple compared with single mild TBI cases.

III: Postconcussion Syndrome

In the data analysis there were a small number of athletes in whom persistent postconcussion symptoms developed, and these individuals were unable to return to play for an extended period. Often the postconcussion symptoms were seen 1 or more weeks after the injury. The postconcussion syndrome follows head injury that is usually mild, and consists of any combination of the symptoms and signs that occur after mild TBI. The Committee decided to analyze the data obtained in players in whom postconcussion syndrome was diagnosed.⁷

When does cerebral concussion end and postconcussion syndrome begin? Very few data are available on the evolution of head injury to postconcussion syndrome in athletes. The purpose of this part of the study was to compare the small group of NFL players who did not return for more than 7 days after a mild TBI with the majority of NFL players who do return within 7 days. The 7-day dividing line between the groups does not reflect an arbitrary distinction. Because NFL teams play games once a week, the players in this study cohort all missed at least one game. The NFL teams play only 16 games per season. Therefore, missing one game involves a significant loss of playing time. The study cohort all had significant functional impairment caused by mild TBI.

There were 72 cases with more than 7 days away from

play among the 887 cases of mild TBI analyzed between 1996 and 2001. Of these injuries, 38 were single concussions experienced in the study period, eight were the first of repeated concussions, 16 were the second, seven were the third concussion, and so on in the study period. The median duration between the first injury and 7 or more days away from play was 364 days, and the median duration between the last injury and 7 or more days away was 329 days, which is statistically similar.

For the whole sample, there were 650 players who experienced 887 concussions during the study period, and the position they were playing was recorded in this analysis. Individually, the position groups most often associated with loss of 7 or more days are the defensive secondary (23.6%), kick unit (19.4 %), quarterbacks (12.5%), and wide receivers (12.5%). The fraction of players in a position with 7 or more days away from play compared with all in that group was highest for the quarterback (14.8%), the return unit on special teams (11.8%), and the secondary (10.8%), followed by the kick unit (10.4%) on special teams. Quarterbacks had the highest odds ratio of 7 or more days away from play with concussion, whereas running backs had the lowest relative risk.

The majority of players with concussions (88.9%) are rested, with 7 or more days out, compared with 90.7% with fewer than 7 days out. Overall, the data show a conservative treatment of concussion. There was no statistical difference in players' treatment in comparisons between the two groups.

Between the initial examination and the first follow-up review, most of the signs and symptoms started to decrease, except for increases in the general category of memory problems, fatigue, irritability, and sleep problems. By the fourth follow-up examination (median 4.7 days), all memory and cognitive problems had cleared. Nevertheless, some players still reported headaches, dizziness, and photophobia. Somatic complaints continued in some players, including personality change and fatigue. By the seventh examination (median 13 days) only headaches remained to clear.

The data analysis allowed the development of profiles for two groups of NFL players with concussions. The first group is the small minority of players who ultimately do not return to play for 7 or more days postinjury. They are more likely to experience LOC as a result of the head injury, and they are more likely to be hospitalized on the day of the injury. At the time of the initial evaluation, these players have a significantly increased number of the signs and symptoms of mild TBI. On initial examination, they are very likely to have retrograde amnesia, difficulties with immediate recall, and overall difficulties with cognition and general memory.

The results of this study and the previous ones prompted the Committee to perform a critical analysis of the widely promoted guidelines for the evaluation and management of concussion in sport. This 6-year study indicates that no NFL player experienced second-impact syndrome, chronic cumulative injury, or chronic traumatic encephalopathy from repeated injuries. These are a few of the expressed rationales for developing management guidelines. The proponents of these guidelines recommend grading the severity of concussion by a limited number of criteria, such as presence or absence of LOC, post-

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traumatic amnesia at time of injury, confusion, and mental status changes soon after injury. The guidelines then make clinical management recommendations on the basis of the grade of concussion diagnosed using these criteria.

Analysis of the NFL data reveals that there are other prognostic factors of equal importance that are not included in the grading systems. These include photophobia, fatigue, and increased absolute numbers of signs and symptoms. Furthermore, the grading systems do not take into account factors such as the position played by the injured athlete and the type of play during which the injury occurred. In the NFL study we found that the presence of signs and symptoms such as fatigue, sleep disturbance, irritability, and/or cognitive or memory impairments on examination the day after the injury also has significant prognostic usefulness. None of the grading systems incorporate results from examinations performed other than on the day of the injury. Although the grading systems use some important prognostic findings, they are limited in their scope and fail to incorporate a number of other factors that have been demonstrated to be predictors of delayed recovery.

The NFL studies also support the contention that grading concussions immediately after injury is prone to error. A number of players with signs and symptoms suggesting a poor prognosis in fact recovered very quickly and returned to play on the day or within a few days of injury. Conversely, there were two players with minimal signs or symptoms, suggesting a good prognosis, who were ultimately kept out of play for 7 or more days after mild TBI. None of the prognostic factors or combinations of factors was 100% accurate in predicting recovery.

It followed from this analysis that the current attempts to link prospective grading of concussion symptoms to arbitrary, rigid management decisions are not consistent with scientific data. We believe that if one insists on grading concussion severity, the best way is retrospectively, on the basis of how long it actually takes the player to become asymptomatic, with normal results on neurological examination. It is the recommendation of the NFL's Committee on Mild Traumatic Brain Injury that team physicians treat their players on a case-by-case basis, using their best clinical judgment and basing their decisions on the most relevant, objective medical data obtained.

IV: Neuropsychological Testing in Evaluating Mild TBI

The development and use of neuropsychological testing in the NFL has been rapid, and it has contributed to the implementation of this testing in other professional sports organizations, including ice hockey, automobile racing, and Australian Rules football. When used in concert with other medical information, neuropsychological test data contribute quantitative information regarding neurocognitive processes, such as attentional, memory, and cognitive processing speed. Neuropsychological testing can provide objective information regarding the recovery process and allows comparisons of the athlete's performance against normative data and the individual's preinjury level of performance.

The NFL's neuropsychological testing program was established as a clinical research program with the goal of investigating the use of such testing to assist team physi-

cians in the return-to-play decision. Athletes in the NFL who underwent neuropsychological testing between 1996 and 2001 and who participated in the study were included. Preseason normative data were collected in 655 NFL athletes. The overall sample of injured players who underwent testing consisted of 143 athletes. This sample represented 22% of the 650 NFL athletes who experienced 887 concussions during the study period. Because participation in the study was voluntary, not all athletes with mild TBI completed neuropsychological testing.

This study supports previous research that has shown that on-field signs of cognitive impairment, such as amnesia, are useful in determining the severity of brain injury.⁴ Players identified as having cognitive and memory disturbances are likely to show neuropsychological impairments on follow-up testing. Athletes with no clinically recognized cognitive and memory impairments on physician examination did not, as a group, have more subtle changes in cognitive processes that were missed during the sideline clinical examination. This suggests that the on-field evaluation by team physicians is effective with regard to the identification of cognitive and memory impairments immediately after an injury.

On review of the data, the fact that there were no overall significant differences in test results between a group of injured NFL athletes who had previously undergone baseline neuropsychological testing suggests that NFL athletes with mild TBIs recover quickly after injury (Fig. 6). In contrast to previous studies in which cognitive difficulties lasting 1 week or more were suggested, NFL athletes demonstrated generally intact performance within several days relative to baseline performance levels.

The issue of the potential cumulative effects of sportsrelated mild TBI has been a particularly controversial one, and many studies have offered different views on the significance of multiple injuries. In this study we did not find a pattern of worse neuropsychological test scores in a group of professional athletes who received close followup care for 6 years. We also did not find worse neuropsychological performance in NFL athletes who were held back from play for 7 or more days compared with a group who returned within 1 week. It is noteworthy that in this group that was kept from play for 7 or more days, the results of neuropsychological tests and medical evaluation of cognitive and memory function were normal within several days of the injury. The results of this study indicate no evidence of worsening injury or chronic cumulative effects of multiple mild TBIs in NFL players.

On the basis of this study, the NFL's Committee on Mild Traumatic Brain Injury makes the following recommendations regarding the proper role of neuropsychological testing in the NFL. Neuropsychological testing is a tool that can assist the physician in evaluating and managing mild TBI. It definitely should not be used in isolation and cannot replace and should not be used to replace the clinical judgment of the treating physician in the diagnosis and management of mild TBI. The main value of neuropsychological testing in this setting is its ability to confirm and corroborate the results of clinical and mental status evaluation.

V: The ImPACT Program

Concussion in professional football

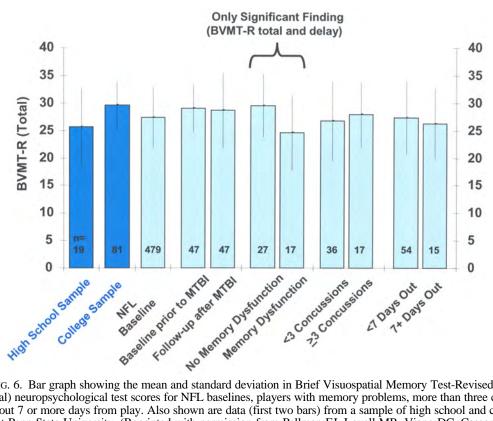


Fig. 6. Bar graph showing the mean and standard deviation in Brief Visuospatial Memory Test-Revised (BVMT-R) (Total) neuropsychological test scores for NFL baselines, players with memory problems, more than three concussions, and out 7 or more days from play. Also shown are data (first two bars) from a sample of high school and college players at Penn State University. (Reprinted with permission from Pellman EJ, Lovell MR, Viano DC, Casson IR, Tucker AM: Concussion in professional football: neuropsychological testing—part 6. Neurosurgery 55: 1290–1305, 2004.)

Despite the initial findings, based on neuropsychological testing, that NFL players had a rapid return to baseline after a mild TBI, the Committee was aware that this was in contrast to several studies that found more long-lasting neuropsychological decrements in high school athletes. Members of the committee decided to perform an additional study, in which professional and younger athletes were compared using the same protocol and identical neurocognitive test battery.3

The ImPACT program is a computerized neuropsychological testing instrument used by some within the NFL neuropsychology program. The ImPACT program (version 2.0) consists of six neuropsychological tests designed to target different aspects of cognitive functioning, including attention, memory, processing speed, and reaction time. The results of ImPACT testing on NFL and high school players were compared.

In this study,3 we found no significant neurocognitive deficits in the NFL sample within the 1st week postinjury, suggesting that NFL athletes with mild TBIs recover relatively quickly after injury. In contrast, we found residual difficulties in reaction time and memory in the high school sample but not in professional players. This raises the question of differential response to mild TBI in professional and high school athletes.

VI: Return to Play

There were concerns based on the results of the earlier studies of mild TBI that perhaps some players were being

returned to play too soon after injury, thus resulting in more prolonged postconcussion syndrome and perhaps creating the risk of more severe brain injury. The committee therefore decided to do a data analysis on NFL players who returned to play on the same day as their mild TBI.6

In the NFL players studied between 1996 and 2001, there were 135 (15.2%) who returned to play immediately after mild TBI and 304 (34.3%) who rested and returned to the same game after concussion. There were few differences in the player position or team activity related to the injury or action taken. However, players who suffered concussions and returned to the same game had fewer initial signs and symptoms than those who were removed from play.

Widely used concussion management guidelines state that athletes can return to play on the day of the injury if they become asymptomatic and if results of examinations performed within 15 minutes of their injury are normal. In the NFL database, 41% of players returned to the same game either immediately or after resting more than 15 minutes. Of those who returned immediately, 17.9% were out more than 15 minutes, and 51.7% of those who rested and returned were out for more than 15 minutes. The data showed no increased risk of repeated mild TBI, prolonged postconcussion syndrome, delayed return to play (≥ 7 days out), second-impact syndrome, or catastrophic intracranial event. The NFL experience thus supports the suggestion that players who become asymptomatic and have normal results on examinations performed at any time after injury, while the game is still in progress, have

E. J. Pellman and D. C. Viano

been and can continue to be safely returned to play on that day. The data also support the proposition that players who experienced LOC had no increased risk of repeated mild TBI or prolonged postconcussion syndrome compared with other players.

The results of this study indicate that many NFL players can be safely allowed to return to play on the day of the injury after sustaining a mild TBI. These players had to be asymptomatic, with normal results on clinical and neurological examinations, and be cleared by a knowledgeable team physician. There were no adverse effects, and the results once again are in sharp contrast to the recommendations in published guidelines and the standard of practice of most college and high school football team physicians. This data analysis was performed on information obtained in adult professional football players, and these findings are not meant to be carried over to any other patient population, including high school and college football players.

Conclusions

The NFL study was conducted to increase the scientific information available to physicians and sports professionals based on prospective clinical information and contemporary, "real-time" biomechanical data. The NFL's Committee on Mild Traumatic Brain Injury is currently supervising work on an animal model of mild TBI, mouthpieces, and studies of retired players that we hope will continue to add information and shed light on the complicated clinical syndrome of mild TBI in athletes.

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EXHIBIT 60





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Michigan Football Woes Jameis Winston's Hometown LeBron's Summer Diet

The Case Against The NFL

Wednesday, February 29, 2012 12:58 pm | Written by: Patrick Hruby







An attorney by training and a member of Congress by trade, Linda Sanchez knows verbal dissembling - read: pure, unadulterated bull excrement - when she hears it, Case in point? During a 2009 Capitol Hill hearing on brain trauma in the National Football League that included commissioner Roger Goodell, the Democratic representative from California introduced a 2007 video clip from HBO's "Real Sports" featuring neurologist Ira Casson, then the co-chair of the league's panel on head injuries.

Interviewer: Is there any evidence, as far as you're concerned, that links multiple head injuries among pro football players with depression?

Casson: No.

Interviewer: With dementia?

Casson: No.

Interviewer: With early onset of Alzheimer's?

Casson: No.

Interviewer: Is there any evidence as of today that links multiple head injuries with any long-term problem like that?

Casson: In NFL players?

Interviewer: Yeah.

Casson: No.



"[The NFL's] actions smacked of them knowing it was a very serious problem," Sanchez says. "And them trying to deny it and cover it up with very vague-sounding and un-alarming information, because, let's face it, there's a heck of a lot of money at stake. If they could deny and delay anybody putting this together, then they could avoid being held liable for these former players suffering these very severe

"It reminded me of the tobacco industry, who knew for years and years that smoking wasn't good for you but kept denying it."

No. No. No. No more, Last week, the family of Dave Duerson - the former Chicago Bears safety who committed suicide by shooting himself in the heart, the better to preserve his brain for scientific study -

filed suit against the NFL, contending that the league's mismanagement of Duerson's on-field concussions resulted in his brain damage and ultimate death. Hundreds of other former players have filed similar suits since last summer, seeking recompense for football-induced headaches and memory loss, depression and dementia, emotional turmoil and cognitive decline. Each complaint alleges essentially the same thing: The NFL knew there was a problem. Knew that concussions can and do produce serious, long-term harm. Knew this and did nothing - failed to adequately warn players about the risk, failed to protect them with proper care and treatment, failed to help when they later became ill, once-robust men laid irrevocably low by the ticking time bombs exploding inside their heads. Worse still, the league knew and pretended otherwise, plausibly denying and implausibly lying and actively covering up, hiding behind phony prudence and junk science, slow-walking the issue into the dank corner of a dark closet, raking in billions all the while, just like Big Tobacco before them.

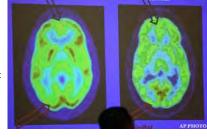
says otherwise. Firmly and consistently, the league claims it handled concussions the best it could given the medical information available at the time; moreover, it intends to fight the lawsuits, four of which have been consolidated in a Philadelphia federal court. Chances are, the league will prevail. It has money. It has lawyers. It has the kind of lawyers that money buys. The NFL can afford to make the battle long, costly and technical; according to sports law expert Michael McCann, it can make a strong defensive case in terms of strict legal culpability. But never mind that. Even if the league wins in court – even if it escapes a potentially damning future discovery process unscathed - it already has lost. Lost whatever remains of its carefully burnished cultural sheen, its implicit, NFL Films-fueled claim to be something greater than big-budget human cockfighting, a red-blooded, all-American enterprise that can kick off the Super Bowl with a pious recitation of the Declaration of Independence while maintaining a straight face. Because the NFL doesn't just have a legal duty to the helmet-smashing men who make its profits possible. It has a moral duty, too. And on that front, the league has failed.

Failed miserably, in fact,



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Start with the science. Medical research dating back to the 1920s indicates that suffering multiple blows to the head that are not allowed to properly heal can result in degenerative and irreversible cognitive impairment – known in boxing as "punch drunkenness." Yet despite presiding over a violent contact sport in which both concussions and sub-concussive head hits are *de rigueur* – and that's just during practice -- the NFL did not formally begin to investigate the issue until 1994, when the league formed its Committee on Mild Traumatic Brain Injury. Heading the group? Former New York Jets team doctor Elliot Pellman. Not a neurologist. A rheumatologist. A man who claimed in his biographical material that he had a medical degree from the State University of New York at Stony Brook, when in fact he reportedly attended medical school in Guadalajara, Mexico. A man who shared the following moment with concussed Jets receiver Wayne Chrebet during a 2003 game against the New York Giants, later detailed by ESPN writer Peter Keating in a chilling magazine article:



"There's going to be some controversy about you going back to play." Elliot Pellman looks Wayne Chrebet in the eye in the fourth quarter of a tight game ... A knee to the back of the head knocked Chrebet stone-cold unconscious a quarter earlier, and now the Jets' team doctor is putting the wideout through a series of mental tests. Pellman knows Chrebet has suffered a concussion, but the player is performing adequately on standard memory exercises.

"This is very important for you," the portly physician tells the local hero, as was later reported in the New York Daily News. "This is very important for your career." Then he asks, "Are you okay?"

When Chrebet replies, "I'm fine," Pellman sends him back in.

Appearing on HBO's "Inside the NFL" that same year, Pellman flatly dismissed a study linking multiple concussions with depression among former players. Months later, Pellman and his colleagues produced a paper stating that there was "no evidence" that concussions produced "permanent or cumulative" damage; in 2006, they published a summary of their work to date, declaring "mild traumatic brain injuries" — read: concussions — "in professional football are not serious injuries."

Read that again: concussions do not qualify as a serious injuries. Are these the kind of doctors you want looking after your son?



Unsurprisingly, independent medical scientists found serious fault with the committee's methodology and conclusions. So did Sanchez. One reason? Pellman and company drew many of their conclusions from voluntary surveys that had been mailed out to a small number of retired players. "A lot of these players who are suffering, they have dementia or are living on the street," Sanchez says. "They don't have the wherewithal to full out a survey. They don't have an address. So the results were very skewed, showing there wasn't a problem. That made me sick to my stomach."

Likewise, independent research contradicted the NFL committee, demonstrating that multiple concussions significantly increased players' risk of cognitive disease and impairment. For example, a 2005 study of over 2,550 former players found that individuals who had suffered three or more concussions during their pro careers were five times more likely than retirees without a history of concussions to be diagnosed with a loss of brain function affecting memory, thinking, language, judgment and behavior.

How did the NFL respond? Think Phillip Morris. Committee member Mark Lovell attacked the above study, claiming that the league wanted to "apply scientific rigor to this issue to make sure that we're really

getting at the underlying cause of what's happening ... you cannot tell that from a survey." (Right. Because surveys aren't credible, unless paid for by the league). Time and again, committee members denied a link between concussions and cognitive decline. They asked for more time to study the issue. They claimed that independent scientists were drawing premature conclusions. In 2007, some of those same independent scientists gave face-to-face presentations to committee members; afterward, the NFL released a statement that in part read:

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Current research with professional athletes has not shown that having more than one or two concussions leads to permanent problems ... It is important to understand that there is no magic number for how many concussions is too many.

The worst example of the league's see-no-evil approach came when forensic pathologist Dr. Bennet Omalu dissected the brain tissue of dead NFL players such as Pittsburgh Steelers Hall of Fame center Mike Webster. Omalu published an article in the academic journal Neurosurgery concluding that football-related head trauma caused the players to suffer the mind-destroying disease chronic traumatic encephalopathy (CTE). Pellman and two other committee members didn't just blow Omalu off — they wrote a letter to the journal attempting to discredit his research. According to a scathing 2009 GQ magazine article, the NFL repeatedly dismissed Omalu before sending an independent expert to examine his work in 2008. The expert, neuropathologist Peter Davies, initially was skeptical — that is, until he saw Omalu's slides, which contained the brain tissue of once-mad, now-deceased football players. "The credit must go to Bennet Omalu," Davies told the magazine. "Because he first reported this and nobody believed him, nobody in the field, and I'm included in that. I did not think there was anything there. But when I looked at the stuff, he was absolutely right. I was wrong to be skeptical."

The NFL's response? According to the magazine, the league declined to make Davies' report public and never spoke to Omalu again. One year earlier, however, it did give active players a pamphlet asserting that the link between concussions and long-term brain damage remained an open question — a position the NFL finally disavowed in 2010, in the wake of its public shaming before Congress and concurrent with new members of a reconstituted concussion committee publicly blasting their predecessors' work as "unacceptable."

Speaking of said predecessors: Also in 2010, Casson finally appeared before Congress in person at a follow-up hearing in Detroit. Having resigned his position on the NFL concussion committee – probably not a coincidence, given that former players disparagingly referred to him as "Dr. No" – he nevertheless doubled-down on his public assertion that there wasn't enough "valid, reliable or objective" scientific evidence to link repeated football head trauma and long-term brain damage. Sanchez was incredulous. When she asked Casson if the link between getting hit in the head and brain damage was

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a generally accepted medical principle, the doctor refused to answer directly, but did note that he wasn't "saying that concussions are good for you."

"That was the strongest thing I could get him to say," Sanchez says. "And he was employed by the NFL to study this. I can't put into words how shocking that was."

By denying the obvious -- that concussions are, in fact, profoundly not good for you -- the league may have reduced its legal culpability in the current wave of lawsuits. As a leading brain scientist told ESPN's Keating, "They're basically trying to prepare a defense for when one of these players sues ... they are trying to say that what's done in the NFL is OK because in their studies, it doesn't look like bad things are happening from concussions." But the NFL also did its players a grave, unforgivable



disservice. Remember Chrebet? After suffering multiple concussions over the course of his football career, he retired in 2005; two years later, he was still suffering from headaches and lethargy. Or take Dave Pear. A former Pro Bowl defensive tackle and Super Bowl winner with the Oakland Raiders, the 58year-old Washington state resident still remembers how concussions in pro football were handled in the 1970s. "If you even talked about them, you were less than a man," he says. "You got knocked out, they held out four fingers. You'd say two. They would say, 'Close enough, get back out there.' There just wasn't a whole lot of concern about our heath."

Since 2004, Pear has been unable to work, instead collecting federal disability payments. The reason? It isn't his creaky spine, even though that has been operated on. It isn't his ruined hips, both of which have been replaced. It's his damaged brain. Eight years ago, a clinical psychologist concluded that Pear had "significant memory impairment as the result of repeated head injuries" and possibly was displaying "signs of early onset dementia." Today, he suffers from vertigo, chronic headaches and short-term memory lapses. Even during the day, he has a hard time staying awake. "I try to keep my mind active," he says. "I read a lot. But with head injuries, it doesn't get better. You just try to maintain some level so you can function. The reality is, it's your wife and your children that pay the biggest price."



The potential price worries Nate Jackson. A Denver Broncos tight end from 2003 to 2008 - the same time period as the NFL's most adamant concussion stonewalling -- Jackson always measured football in terms of its rewards. Money. Women. Status. Pride. A irresistible grab for ephemeral glory, no matter now badly his body ached. "As a player, you don't keep your best interests in mind," he says. "There's always something more powerful pulling you back on the field. When everybody tells you that this athletic talent you have is very, very important, well, what are you without it? How do you step outside of that and think rationally?"

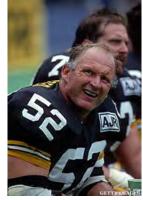
While catching a pass during a 2008 game, Jackson was hit in the head by Cleveland linebacker Willie McGinest. The shoulder-to-helmet blow knocked Jackson out. Almost certainly concussed, he was never diagnosed with a brain injury. Nor was he tested for one. He didn't think to ask. Didn't want to

know. "The [team doctors] knew I was [expletive] up," Jackson says. "They saw the hit. The trainer was telling me not to move my neck. But I intentionally made as little of a deal as I could about it. I didn't want to go sit in a training room. This was before concussions were a big deal. They weren't stressed to us. No specific meetings about it. No points of emphasis from the coaches."

Jackson spent the next three days in bed. Now out of football and writing a book about his experience, he wonders if the blow - or countless others like it - will come back to haunt him. "As a tight end, every day I had to smack my head into another dude's head, over and over again," he says. "I don't know if it's my imagination, but I feel like I can literally feel my brain getting kicked in when I read about concussions. It's a scary thought to consider where I might be in 20 years."

During this year's Super Bowl, the NFL aired a 60-second commercial about player safety, a slick spot in which the evolution of the game and its rules unfolded over the course of a single kick return, one era morphing into the next. Leather helmets became plastic. Players acquired facemasks. At the end of the spot, Baltimore Ravens linebacker Ray Lewis intoned, "Here's to making the next century safer and more exciting. Forever forward. Forever football." Maybe so. But missing from the ad was the league's brain trauma dissembling morphing into acceptance. Casson's no becoming a yes. In the here and now, the NFL touts its born-again concussion religion. A public crackdown on helmetto-helmet hits. Universal return-to-play guidelines for players who have been concussed. Big, bright, liability-limiting posters, right there on locker room walls, stating that concussions can lead to devastating long-term cognitive damage. The league even donates money to medical researchers dissecting ex-players' brains, the same kind of research it once pooh-poohed.

All of that is good. But none of it is enough. Not when Cleveland quarterback Colt McCoy is concussed from a brutal, helmet-to-chinstrap hit in a game last December — and then sent back onto the field in the same game, potentially risking his life, because no one on the Browns medical staff noticed. Not when the league reportedly wanted to insert a concussion liability waiver into new player contracts, starting with this year's draft. (A league spokesman denied the report). And not when hundreds, maybe thousands, of brain-damaged former players need so much help, financial and otherwise, assistance they shouldn't have to go to a courtroom to secure.



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"The NFL doesn't walk away from this issue looking like a standup league," Sanchez says. "They just don't. They're moving in the right direction, but the fact remains that here are guys who are really, seriously messed up, health-wise, continuing to struggle and the league continues to ignore that. They have to go back to the guys that didn't make millions of dollars when they played. They have got to make it right by them."

Pear concurs. He says he made just over \$600,000 in his pro football career. He says he has spent all of it and more on medical bills. A plaintiff in one of the concussion lawsuits, he isn't looking to make a quick buck. He's simply trying to survive. "I'm going to have medical bills the rest of my life from playing football," he says. "I want to be compensated for what the NFL has put myself and my family through. I want to see all my football brothers compensated. I want to see the NFL be to be honest about the sport. It's hazardous to your health."

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Occupy The Marlins

A few years ago, Pear's phone rang. Goodell was on the line. He wanted to talk. Pear says he had been getting a bureaucratic runaround from league and players association disability services, that he needed help and had gotten nowhere. He also runs a blog that acts as a kind of clearinghouse and group therapy session of for retired players, many of them disaffected and struggling, some of them now concussion plaintiffs as well. The commissioner wanted to know what the problems were, and how he could help. "I made him listen to my grievance for 25 minutes," Pear recalls. "He

kept trying to get off the line, getting more and more exasperated. Finally, he said, 'Who do you think I am, God?'"

Pear pauses.

"I said, 'No, Roger, you're the commissioner of the National Football League. It's your duty to protect the integrity of the game. You need to clean up this

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EXHIBIT 61

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http://www.nfl.com/news/story/09000d5d8017cc67/article/nfl-outlines-for-players-steps-taken-to-address-concussions

NFL outlines for players steps taken to address concussions

National Football League

Published: Aug. 14, 2007 at 07:08 p.m. Updated: July 26, 2012 at 08:55 p.m.

The National Football League has outlined for NFL players, coaches, and staff members the recent steps that have been taken to address the management of concussions in the NFL.

"We want to make sure all NFL players, coaches and staff members are fully informed and take advantage of the most up-to-date information and resources as we continue to study the long-term impact of concussions," Commissioner Roger Goodell said. "Because of the unique and complex nature of the brain, our goal is to continue to have concussions managed conservatively by outstanding medical personnel in a way that clearly emphasizes player safety over competitive concerns."

The recent steps were outlined in a memo that will be sent to all NFL players and team personnel with other information. They include the following:

- The NFL held a medical conference in June on the subject of concussions. It was attended by team physicians and athletic trainers from every NFL team and by active players and medical representatives of the NFL Players Association. The conference reviewed the current medical and scientific research and included presentations by doctors and scientists from within and outside the NFL.
- An informational pamphlet on concussions for NFL players and their families has been prepared (below). It describes the symptoms of concussions, what NFL players should look for in themselves or a teammate if they suspect a possible concussion, and what NFL families should know about concussions.
- The establishment of a hotline to report information on a confidential basis about an NFL player being forced to practice or play against medical advice. The hotline underscores the league's priority on player safety over competitive concerns.

The NFL and NFLPA medical advisors prepared a summary of key factors in deciding when NFL players can safely return to the same game or practice. These factors have been identified in medical studies and are used by NFL team medical staffs. They emphasize that concussions in the NFL should continue to be managed conservatively and include the following specific points:

- 1. The player should be completely asymptomatic and have normal neurological test results, including mental status testing at rest and after physical exertion, before returning to play.
- **2.** Symptoms to be taken into account include confusion, problems with immediate recall, disorientation to time, place and person, anterograde and retrograde amnesia, fatigue, and blurred vision.
- 3. If an NFL player sustains a loss of consciousness, as determined by the team medical staff, he should not return to the same game or practice.
- **4.** NFL team physicians and athletic trainers will continue to exercise their medical judgment and expertise in treating concussions, including considering any history of concussions in a player.
- Neuropsychological testing has been expanded for all NFL players. NFL players who have been removed from a game due to a concussion will be re-tested during the season as part of the medical staff's treatment of the player and to assist in determining when players can return to practice and play. Each club will select the neuropsychological testing provider of its choice.
- Player safety rules relating to the use of the helmet will continue to be closely enforced. This will include strict enforcement of the requirement that chin straps on helmets be completely and properly buckled so that the helmet provides the maximum protection.

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· The NFL will continue to research and study all elements of concussions with a particular focus on long-term effects.

BELOW IS AN EXCERPT FROM THE NFL PLAYER CONCUSSION PAMPHLET:

What is a Concussion? It's More Than a "Ding."

Concussions are caused by a hard hit to the head. The hit is typically from another player's helmet, shoulder pad or knee or from a fall to the ground. The effects usually last a short time, but it's important that they are treated properly and promptly by you, your team doctors and your athletic trainers.

You shouldn't decide if it is just a "ding." Instead, you should report any symptom from the list below to your medical staff. This will help determine whether or not you have had a concussion.

"Ding" is not a medical term. It doesn't describe specific symptoms and won't help your medical staff. Try to describe your symptoms from the following list.

How do I know if I have had a concussion?

These are some of the symptoms you may experience immediately or within a few days of having a concussion. Every concussion is different, players may react differently and not all players will experience the same symptoms.

The most common symptoms are:

- · Imbalance: You may feel a change in your sense of balance, feel dizzy, or unsteady on your feet.
- **Headache:** This is the most common symptom with concussion. It may be mild to severe in intensity and you may feel like there is pressure in your head. This may be accompanied by nausea and vomiting.
- Confusion: You may be confused about where you are, about a play, the score or game situation. You may not remember the play you are running.
- **Memory loss:** You may lose memory about things that happened BEFORE or AFTER you were hit. You may not remember what happened during the play or the quarter before your collision. Or you can't remember what happened on the field or on the sidelines after your hit. You may ask the same questions over and over again.
- · Loss of consciousness: You may black out or get knocked out, even for a second or two.
- **Vision change:** You may become sensitive to light, have blurred vision, double vision or feel like lights seem brighter. Some athletes also report "seeing stars" or other objects following a hard hit.
- Hearing change: You may feel a change in your hearing so sounds suddenly seem very loud, or you may hear a high pitch tone in your ears.
- **Mood change:** You may have a sudden change in your mood or a teammate may notice a change in your mood following a collision. For example, you might suddenly start to laugh or cry for no reason. You may not know this is happening but teammates, coaches, or the medical staff may see it. After a game, you may feel more irritable, anxious, or cranky than usual.
- Fatigue: You may feel more exhausted than usual after a game when you had a hard hit to the head. Some athletes report that they need to sleep many more hours after a concussion.
- · Malaise: You may just "not feel right" but can't point to a specific problem.

Not every hard hit to the head leads to a concussion and whether or not you have a concussion can only be determined by your team doctors and athletic trainers. If the team medical staff does not know that you are injured, it can't help you!

You may not always recognize your symptoms. But your teammates, coaches or family members may see a difference in you that you don't. If someone sees a change in you, take it seriously and report it to your team medical staff.

What should you report to your team medical staff?

Don't try to make a diagnosis yourself. A concussion needs to be diagnosed by your team medical staff. If you have had a

hard hit to the head and have symptoms, you should immediately report your symptoms to your team doctors and athletic trainers, who will conduct a thorough evaluation on the sideline.

On occasions, symptoms from concussion will be more obvious or noticeable hours after the impact. Symptoms should be reported to your medical staff regardless of when you become aware of them.

If you see any symptoms in a teammate, tell your team doctors or athletic trainers because your teammate may not always realize he has had a concussion.

When should I return to play following a concussion?

After a concussion, all return-to-play decisions should be made by your team medical staff. These decisions should never be made by players or coaches. You should be free of symptoms before you return to play.

If you have had a concussion and feel you are being pressured to return too quickly, or think that is happening to a teammate, you can call (the hotline number) to make a confidential report.

Am I at risk for further injury if I have had a concussion?

Current research with professional athletes has shown that you should not be at greater risk of further injury once you receive proper medical care for a concussion and are free of symptoms.

If I have had more than one concussion, am I at increased risk for another injury?

Current research with professional athletes has not shown that having more than one or two concussions leads to permanent problems if each injury is managed properly. It is important to understand that there is no magic number for how many concussions is too many.

Research is currently underway to determine if there are any long-term effects of concussion in NFL athletes.

What is the treatment for a concussion?

The treatment for concussion usually consists of rest. Medication may sometimes be prescribed by your team doctors for symptoms such as headaches and dizziness. If your team doctor prescribes medication, be sure to follow his directions and those provided with the prescription.

It is important that you avoid drinking alcohol. Also, if you intend to use over-the-counter medication, vitamins or supplements, tell your team doctors. They may want you to stop taking them.

You should avoid caffeine and make sure that you do not become dehydrated.

EXHIBIT 62

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Racial/Ethnic Disparities in Mortality by Stroke Subtype in the United States, 1995–1998

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Healthy People 2010 objectives for improving health include a goal to eliminate racial disparities in stroke mortality. Age-specific death rates by stroke subtype are not well documented among racial/ethnic minority populations in the United States. This report examines mortality rates by race/ethnicity for three stroke subtypes during 1995–1998. National Vital Statistics' death certificate data were used to calculate death rates for ischemic stroke (n = 507,256), intracerebral hemorrhage (n = 97,709), and subarachnoid hemorrhage (n = 27,334) among Hispanics, Blacks, American Indians/Alaska Natives, Asians/Pacific Islanders, and Whites by age and sex. Comparisons with Whites as the referent were made using age-standardized risk ratios and age-specific risk ratios. Age-standardized mortality rates for the three stroke subtypes were higher among Blacks than Whites. Death rates from intracerebral hemorrhage were also higher among Asians/Pacific Islanders than Whites. All minority populations had higher death rates from subarachnoid hemorrhage than did Whites. Among adults aged 25–44 years, Blacks and American Indians/Alaska Natives had higher risk ratios than did Whites for all three stroke subtypes. Increased public health attention is needed to reduce incidence and mortality for stroke, the third leading cause of death. Particular attention should be given to increasing awareness of stroke symptoms among young minority groups. *Am J Epidemiol* 2001;154:1057–63.

Asian Americans; Blacks; cerebral hemorrhage; cerebrovascular accident; Hispanic Americans; Indians, North American; mortality; subarachnoid hemorrhage

Although stroke is the third leading cause of death in the United States (1) and its overall mortality rates are well documented, few studies have addressed racial/ethnic differences in stroke mortality (2–4). In 1997, all racial/ethnic minority populations aged 35–64 years experienced higher

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Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision.

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mortality rates for stroke than did the White population (5). Currently, more than 25 percent of the US population is composed of racial/ethnic minority populations and, by 2050, that percentage should nearly double (6). Thus, there is an increasing need to understand racial/ethnic differences in stroke mortality so that appropriate public health interventions might be developed to eliminate disparities.

In addition, racial/ethnic stroke mortality differentials may exist according to the type of stroke. Ischemic stroke accounts for 70–80 percent of all strokes, but cerebral and subarachnoid hemorrhagic stroke have higher risks of fatality (7). Examining the patterns of stroke subtypes among racial/ethnic populations could help target prevention efforts. In this report, we present national, racial/ethnic, agestandardized, and age-specific mortality rates and risk ratios for stroke subtypes among the major racial/ethnic groups: non-Hispanic American Indians/Alaska Natives, non-Hispanic Asians/Pacific Islanders, non-Hispanic Blacks, non-Hispanic Whites, and Hispanics.

MATERIALS AND METHODS

National Vital Statistics' data for death certificates were used to determine death rates and risk ratios for stroke mortality among persons who were ≥25 years during 1995–1998. In addition to medical examiners and coroners, practicing physicians report the cause of death on the certificates. The death certificates are processed in state vital

statistics offices and then sent to the National Center for Health Statistics at the Centers for Disease Control and Prevention for entry into a national detailed mortality database file (1). Death rates exclude nonresidents. For this study, observed stroke deaths were those for which the underlying cause of death was classified according to the International Classification of Diseases, Ninth Revision (ICD-9), codes 430-438 as listed on death certificates. Stroke subtypes were defined as subarachnoid hemorrhage (code 430), intracerebral hemorrhage (codes 431–432), and ischemic stroke (codes 433-434 or 436-438). Deaths attribbuted to transient ischemic attack (code 435) were excluded, but these events accounted for <1 percent of stroke deaths. There were no deaths listed as ICD-9 code 432 (other or unspecified intracerebral hemorrhage) during this time period. Demographic information, such as age, race, and ethnicity, is reported on death certificates by funeral directors on the basis of observation or information with which they are provided, usually by family members. Since 1992, information on both race and Hispanic origin has been requested on death certificates.

Death rates and risk ratios were calculated for groups defined by race/ethnicity, sex, and age (25-44, 45-64, and ≥65 years). Mortality rates (per 100,000 population) for the 4-year period 1995-1998 were calculated as the number of deaths divided by the population of interest. Population data (denominators for death rates) were postcensal estimates from the US Bureau of the Census. Age-standardized death rates were calculated by the direct method using the year 2000 standard US population (8). To estimate the overall excess risk for stroke death among racial/ethnic minority populations, we calculated risk ratios and 95 percent confidence intervals by dividing the rate for each racial/ethnic group by the rate for the White population (9). To estimate the excess risk in age groups, the risk ratios and 95 percent confidence intervals were calculated by dividing the mortality rates in each age group by the corresponding White mortality rates (10). Risk ratios of ≥1.0 indicate higher death rates or excess risk for the minority population than for Whites, while ratios of <1.0 indicate a lower rate or risk. Risk ratios are not presented for a category with ≤20 deaths because of potential instability of the estimate. Because the number of deaths in a given year was quite small in some

subgroups, data were combined for 1995–1998 to create more robust estimates.

RESULTS

In 1995–1998, there were 507,256 deaths from ischemic stroke, 97,709 from intracerebral hemorrhage, and 27,334 from subarachnoid hemorrhage among adults aged ≥25 years. Ischemic strokes accounted for 80 percent of deaths from these stroke subtypes (82 percent among non-Hispanic Whites, 75 percent among non-Hispanic Blacks, 74 percent among non-Hispanic American Indians/Alaska Natives, 62 percent among non-Hispanic Asians/Pacific Islanders, and 67 percent among Hispanics). For ischemic stroke, the agestandardized death rate among Blacks (95.8 per 100,000) was 1.30 (95 percent confidence interval (CI): 1.29, 1.31) times or 30 percent higher than the rate for Whites (73.7 per 100,000), while American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic adults had lower death rates than Whites (table 1). For intracerebral hemorrhage, death rates for Blacks and Asians/Pacific Islanders were 1.70 (95 percent CI: 1.67, 1.74) and 1.52 (95 percent CI: 1.47, 1.58) times, respectively, as high as those of Whites. All minority populations had higher rates for subarachnoid hemorrhage than did Whites. Similar racial/ethnic differences were observed among both men and women (figure 1). Black men and women had the highest death rates for all three stroke subtypes, while Asian/Pacific Islander men and women also had high rates for both intracerebral and subarachnoid hemorrhagic stroke.

Eighty-nine percent of ischemic stroke deaths were attributed to acute, ill-defined, cerebrovascular disease (ICD-9 code 436), other and ill-defined cerebrovascular disease (ICD-9 codes 437–437.9), and late effects cerebrovascular disease (ICD-9 code 438) (figure 2). Only 5 percent of ischemic stroke deaths were classified as other (code 437.8) or unspecified (code 437.9). There were no appreciable differences among the racial/ethnic groups in the percentage distribution of these ICD-9 ischemic stroke classifications. When the analysis was repeated excluding these codes, there was essentially no change in the risk ratios.

As expected, the death rates for all three stroke subtypes increased with age among all racial/ethnic populations (table 2). For all three stroke subtypes, Blacks and American

TABLE 1. Age-standardized death rates (per 100,000 population) from stroke subtypes and risk ratios* and 95% confidence intervals comparing rates in racial/ethnic populations with those in White populations among adults aged 25 years or older, United States, 1995–1998

	Ischemic				Intracerebral hemorrhage			Subarachnoid hemorrhage				
	No. of deaths	Rate	RR†	95% CI†	No. of deaths	Rate	RR	95% CI	No. of deaths	Rate	RR	95% CI
Non-Hispanic												
White	430,749	73.7			75,363	13.2			20,564	3.8		
Black	54,555	95.8	1.30	1.29, 1.31	14,028	22.5	1.70	1.67, 1.74	3,779	5.7	1.50	1.45, 1.55
American Indian/Alaska Native	1,435	48.6	0.66	0.63, 0.69	344	10.4	0.79	0.71, 0.88	161	4.4	1.16	0.99, 1.35
Asian/Pacific Islander	6,599	45.8	0.62	0.61, 0.64	3,173	20.1	1.52	1.47, 1.58	893	5.2	1.37	1.28, 1.46
Hispanic	13,918	39.7	0.54	0.53, 0.55	4,801	12.0	0.91	0.88, 0.94	1,937	4.2	1.11	1.05, 1.1

^{*} Risk ratio compares the rate for a racial/ethnic minority population with the rate for the White population.

[†] RR, risk ratio; CI, confidence interval.

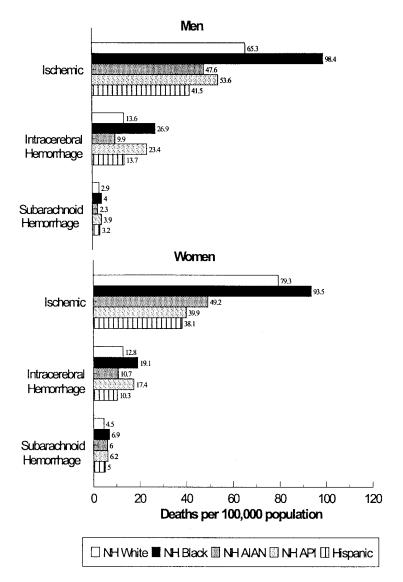


FIGURE 1. Age-standardized death rates (per 100,000 population) for stroke subtype among adults aged 25 years or older, by race/ethnicity and sex, United States, 1995–1998. Death rates per 100,000, age adjusted to the 2000 total US standard population. *International Classification of Diseases*, Ninth Revision, codes for subarachnoid hemorrhage (code 430), intracerebral hemorrhage (codes 431–432), and ischemic hemorrhage (codes 433, 434, 436–438). Transient cerebral ischemia (code 435) was excluded. Categories for race and Hispanic origin (racial/ethnic populations) are mutually exclusive: NH, non-Hispanic; AIAN, American Indian/Alaska Native; API, Asian/Pacific Islander.

Indians/Alaska Natives at younger ages had higher rates of death than did Whites at similar ages; however, the risk of death was similar or lower at older ages. For example, the age-specific rate of intracerebral hemorrhagic deaths among Blacks was 5.20 (95 percent CI: 4.91, 5.51) times greater at ages 25–44 years, 3.94 (95 percent CI: 3.82, 4.07) times greater at ages 45–64 years, but similar (risk ratio = 1.04, 95 percent CI: 1.01, 1.07) at ages ≥65 years compared with the death rate in the corresponding age group of Whites. For intracerebral hemorrhage, the risk of death was higher at younger ages among Hispanics compared with Whites and higher at all age groups for Asians/Pacific Islanders than Whites. For subarachnoid hemorrhage, Asians/Pacific Islanders had a lower risk of mortality at younger ages but a

greater risk at older ages compared with corresponding Whites. The age-specific racial/ethnic differential in each minority population was similar for men and women (data not shown). Both Black men and Black women in the youngest age group, 25–44 years, had substantially higher death rates for all stroke subtypes than corresponding White men and White women.

DISCUSSION

The Healthy People 2010 objectives include a goal to eliminate racial disparities in stroke mortality (11). Death rates for stroke declined by 70 percent overall from 1950 to 1996, but the rate of decline varied by race/ethnicity and

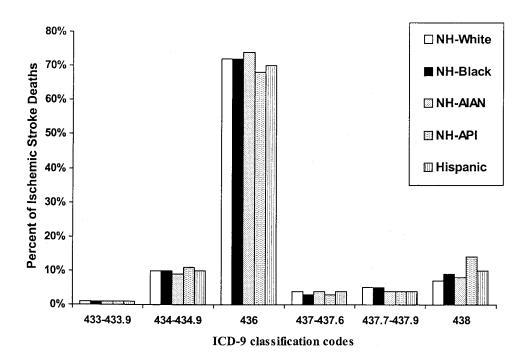


FIGURE 2. Percentage of ischemic stroke deaths in adults aged 25 years or older by *International Classification of Diseases*, Ninth Revision (ICD-9), codes for ischemic stroke (codes 433–434.9, 436–438) and race/ethnicity, United States, 1995–1998. Categories for race and Hispanic origin (racial/ethnic populations) are mutually exclusive: NH, non-Hispanic; AIAN, American Indian/Alaska Native; API, Asian/Pacific Islander.

TABLE 2. Age-specific death rates (per 100,000 population) from stroke subtypes and risk ratios* and 95% confidence intervals comparing death rates in racial/ethnic populations with death rates in the White population, adults aged 25 years or older, United States, 1995–1998

Ethnicity, race,		Ischemic			Intracerebral hemorrhage			Subarachnoid hemorrhage		
and age group (years)	Rate	RR†	95% CI†	Rate	RR	95% CI	Rate	RR	95% CI	
Non-Hispanic										
White										
25-44	0.8			1.0			1.3			
45-64	11.3			6.9			4.3			
≥65	355.1			53.0			8.7			
Black										
25-44	2.8	3.50	3.25, 3.77	5.2	5.20	4.91, 5.51	2.9	2.23	2.09, 2.3	
45–64	38.3	3.39	3.30, 3.48	27.2	3.94	3.82, 4.07	7.1	1.65	1.56, 1.7	
≥65	416.3	1.17	1.16, 1.18	55.1	1.04	1.01, 1.07	9.6	1.10	1.04, 1.1	
American Indian/Alaska Na	ative									
25–44	1.4	1.85	1.25, 2.44	1.6	1.60	1.17, 2.20	1.8	1.38	1.02, 1.8	
45–64	16.7	1.48	1.29,1.69	9.6	1.39	1.17, 1.66	5.3	1.23	0.97, 1.5	
≥65	216.1	0.61	0.57, 0.64	32.8	0.62	0.56, 0.69	8.8	1.01	0.76, 1.3	
Asian/Pacific Islander										
25–44	0.6	0.75	0.59, 2.95	1.4	1.40	1.21, 1.63	1.0	0.77	0.60, 0.9	
45–64	10.1	0.89	0.83, 0.96	13.2	1.91	1.79, 2.04	4.6	1.07	0.93, 1.2	
≥65	215.0	0.61	0.59, 0.62	76.1	1.44	1.39, 1.50	16.1	1.85	1.65, 2.0	
Hispanic										
25–44	0.8	1.00	0.88, 1.13	1.5	1.50	1.37, 1.64	1.3	1.00	0.91, 1.1	
45-64	10.9	0.96	0.92, 1.01	10.4	1.51	1.43, 1.59	5.3	1.23	1.15, 1.3	
≥65	182.0	0.51	0.50, 0.52	39.4	0.74	0.71, 0.77	9.1	1.05	0.96, 1.1	

^{*} Risk ratio is calculated by dividing the age-specific death rates in each racial/ethnic minority group by the corresponding death rates of the Whites.

[†] RR, risk ratio; CI, confidence interval.

halted in the early 1990s before declining again in 1995 (12). Even if death rates continue to fall, however, the aging of the population could mean that the absolute number of deaths will increase. This report and an earlier one (5) suggest an excess risk of dying from stroke at younger ages for minority groups compared with Whites.

Consistent with previous findings (7, 13–19), Black adults were more likely than their White peers to die from ischemic, intracerebral, and subarachnoid hemorrhagic stroke in 1995-1998. Previous reports suggest that racial/ethnic disparities in stroke subtype mortality may be driven by differences in incidence with more new cases occurring among Blacks and Hispanics (7, 20, 21). Community studies in the past 20 years have observed higher incidences of all three stroke subtypes among Black adults (14, 15, 17). Differences in death rates for stroke subtype between minority populations and Whites may reflect socioeconomic status, greater severity of disease and poor survival at younger ages, and variations in risk factors such as obesity, uncontrolled high blood pressure, inactivity, poor nutrition, diabetes, and cigarette smoking (2, 3, 16, 19, 22, 23). Other factors that influence death rates include the lack of access to medical care, which may include lack of health insurance, differential access to or acceptance of invasive procedures, transportation difficulties, and lack of knowledge about early warning signs of stroke (3, 16, 19–26). Deaths from stroke can be delayed or reduced by preventing and controlling these risk factors and by removing barriers to early and effective treatment. Additional targeting of these efforts in minority populations may be needed.

In the present report, we observed that a greater risk of deaths from all stroke subtypes relative to Whites was concentrated below age 65 years for both Blacks and American Indians/Alaska Natives. This pattern of a greater risk of stroke deaths at younger ages was also observed for Hispanics and Asians/Pacific Islanders for death from intracerebral hemorrhage. These racial/ethnic differences among younger adults may in part be explained by racial/ethnic differences in risk factors, especially among younger adults. The Behavioral Risk Factor Surveillance System reported for 1996-1998 that young racial/ethnic minority groups throughout the United States had a higher prevalence of smoking, obesity, and diabetes than did young Whites (24-26), which could lead to our finding of greater racial gaps among Blacks and American Indians/Alaska Natives, aged 25-44 years. A 1993 study in Cincinnati. Ohio, suggested that excess risk of subarachnoid hemorrhage in Blacks could be attributable to their more prevalent risk factors such as hypertension, smoking, alcohol abuse, and unrecognized genetic/environmental factors (15, 17). Furthermore, an earlier onset of obesity, diabetes mellitus, and hypertension in these populations (24-26) may contribute to earlier cerebrovascular vessel damage. In terms of reducing the number of people at risk for the development of intracerebral hemorrhage and ischemic stroke, these findings highlight the importance of both primary and secondary prevention for eliminating racial disparities in the development and management of hypertension, diabetes mellitus, and obesity.

Both intracerebral hemorrhage and subarachnoid hemorrhage account for over half of early age stroke deaths in population-based studies of stroke mortality (13-15). Hemorrhagic strokes are more lethal than ischemic strokes. For example, Medicare patients hospitalized for hemorrhagic stroke were five times more likely to die than those hospitalized with ischemic stroke even after adjustment for age, sex, race, hypertension, diabetes, coronary heart disease, heart failure, atrial fibrillation, stroke types, and length of hospital stay (27). In a national study of Medicare beneficiaries, the racial gap between Blacks and Whites widened from 1990 to 1995 for mortality from hemorrhagic stroke, while the gap for ischemic stroke narrowed (16). Ongoing research on other risk factors is assessing the impact of oral contraceptives, alcohol consumption, antiphospholipid antibodies, increased homocysteine, inflammation, and infection on stroke (28, 29). Eventually, these factors may be found important in explaining disparities in stroke incidence.

The aging of the US population in general suggests that the actual numbers of stroke cases could increase. Minority groups could further experience an increasing burden of stroke. The Bureau of Census estimates that Hispanic and Asian/Pacific Islander populations aged 25 years or older will increase almost 400 percent each from 1995 to 2050, while the American Indian/Alaska Native adult population will increase to 142 percent (6). The Black population is estimated to increase 116 percent by 2050, whereas the White adult population will have the smallest increases (6). Thus, public health programs for the prevention of stroke should place more focus among racial/ethnic minority populations to further reduce overall stroke mortality.

Few studies have examined stroke deaths in American Indians/Alaska Natives and in Asians/Pacific Islanders because their population sizes are small. American Indians/Alaska Natives have a greater prevalence of smoking and obesity, which may result in a higher prevalence of hypertension and diabetes mellitus (24), both of which are stroke risk factors. In our study, American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic groups had a higher mortality at younger ages for some stroke subtypes compared with Whites. Underreporting of American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic origin on death certificates and census population counts can lead to underestimates of the risk of stroke deaths in these groups (6, 30, 31). A report from the National Center for Health Statistics suggests that racial/ethnic reporting biases due to miscoding on death certificates and undercoverage in the census could result in death rates being underreported by as much as 21 percent for American Indians/Alaska Natives, 11 percent for Asians/Pacific Islanders, and 2 percent for Hispanics, as well as slightly overreporting for Blacks (5 percent) (30). Hence, we may have underestimated the racial disparity gaps for American Indians/Alaska Natives, Asians/Pacific Islanders, and Hispanics and may have overestimated the gap for Blacks. There is little reported information about age misclassification on death certificates and in the census. Despite these potential limitations, our results emphasize the need to direct prevention efforts to the most vulnerable groups at risk of stroke mortality, especially among the younger aged minority populations.

Another potential limitation of this study is the accuracy of reporting cause of death using the ICD-9 codes. Historically, during the 1970s and 1980s, the classification of stroke subtypes was not considered very accurate (32). Since the advent of widespread use of computerized tomography, a death certificate diagnosis of intracranial hemorrhage versus nonhemorrhagic stroke appears to be sufficiently accurate for use in epidemiologic studies (33). Nonetheless, our findings suggest that there was no racial/ethnic difference in ICD-9-defined classifications within the stroke subtypes.

Since the 1960s, it is evident that considerable geographic variations in stroke incidence and stroke mortality exist with the highest rates observed in the stroke belt of the southeastern United States (34, 35). The patterns of age-specific excess risk of overall stroke death in the stroke belt differed between Black and White men and women (36). It is beyond the scope of the current paper to examine geographic variations for stroke subtypes between racial/ethnic groups.

Our results suggest the need for greater public health attention to the nation's third leading cause of death and highlight the need for reducing racial/ethnic disparities in stroke mortality, particularly at younger ages. Educating the public about the signs and symptoms of a stroke may be key to preventing premature stroke death among young adults who perceive stroke as a disease of the elderly. Further epidemiologic studies may help to reveal risk factor clustering that operates more specifically for stroke subtypes in those at highest risk in these populations. Targeted research and evaluation among these high-risk populations may also help to identify specific differences between and within subpopulations related to lower socioeconomic or educational levels or to adverse environmental factors.

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EXHIBIT 63

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Demystifying Psychiatry

A resource for patients and families

by Charles Zorumski, M.D., and Eugene Rubin, M.D., Ph.D.

The Financial Cost of Dementia

Most of the costs of treating Alzheimer's disease are not covered by Medicare. Published on October 10, 2013 by Eugene Rubin, M.D., Ph.D. in Demystifying Psychiatry











Eugene Rubin, M.D., Ph.D., is Professor and Vice-Chair for Education in the Department of Psychiatry at Washington University in St. Louis - School of Medicine. more...

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Many of us know the emotional toll that Alzheimer's disease and other dementing illnesses have on patients and families, but how much do we know about the financial burden? A recent report in the New England Journal of Medicine examined the cost of taking care of persons with dementias. Not only are the costs dramatic, but the nature of these costs and who pays the price are sobering.

In 2010 dollars, the cost associated with dementia treatment and care is estimated to be between \$42,000 and \$56,000 per person per year. Because about 15% of persons 70 and older have dementia, the total cost in the US is an astounding \$157 billion to \$215 billion per year. Of this total, Medicare covers only about \$11 billion.

Why so expensive? Over 75% of the cost per individual involves either nursing home or home care costs. Overall, nursing home care accounts for about 25% of the total cost. About 50% of the cost involves home care. This number is derived from either the actual cost of paying for formal home-based care or the cost of lost wages for family members or friends to provide care for a demented person still living at home. We suspect that many are personally aware of the financial and emotional costs of providing care to a parent or grandparent. Dementia care is one side of the "sandwich" of the so-called "sandwich generation."

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Medicare-related costs make up about \$2,700 of the approximately \$50,000 annual cost. Why so low? Medicare-covered costs involve direct medical services. Hospital and physician bills resulting from dementia are a relatively small percent of the total cost of taking care of persons with dementia. Therefore, although Medicare and/or other medical insurance cover the majority of hospital and doctor charges, these bills make up only 5-6% of the total costs.

Most nursing home bills are not covered by Medicare or other third party medical insurance policies. If a person requires long term nursing home care, the costs (about \$80,000 per year) are paid from personal funds unless a person had purchased a very specific type of insurance called long-term care insurance. Once personal savings are fully depleted (i.e., all of a person's savings are gone), Medicaid helps pay nursing home costs. However, it may be difficult to find a Medicaid-subsidized bed in a high quality nursing home.

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available that should allow us to determine who is likely to develop this illness years down the road. With the ability to detect individuals at high risk, research clinicians are already studying medications that might prevent the abnormal brain processes that cause disease progression. The bad news is that therapeutic efforts to date have not been highly successful, and research funding is not keeping up with the potential for clinically significant advances. We would argue that investments in preventing Alzheimer's disease and other dementias should be a very high national priority. We would further argue that there are staggering costs associated with other neuropsychiatric illnesses, including substance abuse, schizophrenia, and depression. In fact, combined costs of these illnesses are perhaps double the costs associated with Alzheimer's disease, yet these are even more underfunded areas of research. Naturally, as academic physicians, we may be biased. What do you think?

This post was written by Eugene Rubin MD, PhD and Charles Zorumski MD

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EXHIBIT 64



George HalasHeight: 6-0 Weight: 182 Deceased Born: 2/2/1895 Chicago , IL College: Illinois Experience: 10 Seasons Hall of Fame Induction: 1963

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Season	Receiving					Rushing				Fumbles					
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Published: Oct. 5, 2014 at 02:16

p.m.
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Published: Oct. 5, 2014 at 01:54

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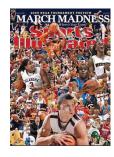
EXHIBIT 65

THE VAULT

How (and Why) Athletes Go Broke

Recession or no recession, many NFL, NBA and Major League Baseball players have a penchant for losing most or all of their money. It doesn't matter how much they make. And the ways they blow it are strikingly similar

Print



BY PABLO S. TORRE

Originally Posted: March 23, 2009 What the hell happened here? Seven floors above the iced-over Dallas North Tollway, Raghib (Rocket) Ismail is revisiting the question. It's December, and Ismail is sitting in the boardroom of Chapwood Investments, a wealth management firm, his white Notre Dame snow hat pulled down to his furrowed brow.

In 1991 Ismail, a junior wide receiver for the Fighting Irish, was the presumptive No. 1 pick in the NFL draft. Instead he signed with the CFL's Toronto Argonauts for a guaranteed \$18.2 million over four years, then the richest contract in football history. But today, at a private session on financial planning attended by eight other current or onetime pro athletes, Ismail, 39, indulges in a luxury he didn't enjoy as a young VIP: hindsight.

"I once had a meeting with J.P. Morgan," he tells the group, "and it was literally like listening to Charlie Brown's teacher." The men surrounding Ismail at the conference table include Angels outfielder Torii Hunter, Cowboys wideout Isaiah Stanback and six former pros: NFL cornerback Ray Mickens and fullback Jerald Sowell (both of whom retired in 2006), major league outfielder Ben Grieve and NBA guard Erick Strickland ('05), and linebackers Winfred Tubbs ('00) and Eugene Lockhart ('92). Ismail ('02) cackles ruefully. "I was so busy focusing on football that the first year was suddenly over," he says. "I'd started with this \$4 million base salary, but then I looked at my bank statement, and I just went, What the. . .?"

Before Ismail can elaborate on his bewilderment--over the complexity of that statement and the amount of money he had already lost--eight heads are nodding, eight faces smiling in sympathy. Hunter chimes in, "Once you get into the financial stuff, and it sounds like Japanese, guys are just like, 'I ain't going back.' They're lost."

At the front of the room Ed Butowsky also does a bobblehead nod. Stout, besuited and silver-haired, Butowsky, 47, is a managing partner at Chapwood and a former senior vice president at Morgan Stanley. His bailiwick as a money manager has long been billionaires, hundred-millionaires and CEOs--a club that, the Steinbrenners' pen be damned, still doesn't include many athletes. But one afternoon six years ago Butowsky was chatting with Tubbs, his neighbor in the Dallas suburb of Plano, and the onetime Pro Bowl player casually described how money spills through athletes' fingers. Tubbs explained how and when they begin earning income (often in school, through illicit payments from agents); how their pro salaries are invested (blindly); and when the millions evaporate (before they know it).

"The details were mind-boggling," recalls Butowsky, who would later hire Tubbs to work in business development at Chapwood. "I couldn't believe what I was hearing."

What happens to many athletes and their money is indeed hard to believe. In this month alone Saints alltime leading rusher Deuce McAllister filed for bankruptcy protection for the Jackson, Miss., car dealership he owns; Panthers receiver Muhsin Muhammad put his mansion in Charlotte up for sale on eBay a month after news broke that his entertainment company was being sued by Wachovia Bank for overdue credit-card payments; and penniless former NFL running back Travis Henry was jailed for nonpayment of child support.

In a less public way, other athletes from the nation's three biggest and most profitable leagues--the NBA, NFL and Major League Baseball--are suffering from a financial pandemic. Although salaries have risen steadily during the last three decades, reports from a host of sources (athletes, players' associations, agents and financial advisers) indicate that:

- By the time they have been retired for two years, 78% of former NFL players have gone bankrupt or are under financial stress because of joblessness or divorce.
- Within five years of retirement, an estimated 60% of former NBA players are broke.
- Numerous retired MLB players have been similarly ruined, and the current economic crisis is taking a toll on some active players as well. Last month 10 current and former big leaguers--including outfielders Johnny Damon of the Yankees and Jacoby Ellsbury of the Red Sox and pitchers Mike Pelfrey of the Mets and Scott Eyre of the Phillies--discovered that at least some of their money is tied up in the \$8 billion fraud allegedly perpetrated by Texas financier Robert Allen Stanford. Pelfrey told the New York Post that 99% of his fortune is frozen; Eyre admitted last month that he was broke, and the team quickly agreed to advance a portion of his \$2 million salary.

The Wall Street meltdown is only the latest threat to athletes' financial health. "Athletes have a different set of challenges from, say, entertainers," says money manager Michael Seymour, the founder of Philadelphia-based UNI Private Wealth Strategies. "There's a far shorter peak earnings period [in sports] than in any other profession, and in many cases they lack the time and desire to understand and monitor their investments."

In 2005 Butowsky began inviting sports figures--some well off, some not--to what he calls his financial "boot camps," elementary sessions that go from defining a bond to explaining a diversified portfolio as the equivalent of a balanced meal. There is no charge for the sessions or pressure to sign up with Chapwood, according to Butowsky, who calls this service his "mitzvah to sports." The financial adviser, who helps counsel Thunder forward Kevin Durant pro bono, hopes merely that the sessions will reflect well upon Chapwood. Such goodwill is easy to earn: The bar for radically improving the financial habits of pro athletes, Butowsky acknowledges, is low enough for a toddler to trip over.

"Oh, I've seen it all," says veteran agent Bill Duffy, whose clients include Suns guard Steve Nash and Nuggets forward Carmelo Anthony. "A pro athlete's money is supposed to outlive his career. Most players never get that."

Why? Where do they go wrong?

I.

The Lure of The Tangible

Over the years Rocket Ismail's portfolio has contained a passel of dubious inventions

and risky investments. After mentioning that he once poured money into a religious movie, the gregarious father of four goes uncharacteristically mum about the details. "I don't really want to go over that agony," he says, smiling thinly.

Ismail played two years in Canada and 10 in the NFL, estimating that he earned \$18 million to \$20 million in salary alone. He made an abortive NFL comeback attempt in 2006, never getting beyond workouts with the Redskins, and then navigated the reality-TV circuit (Pros vs. Joes, Ty Murray's Celebrity Bull Riding Challenge). Today he does a Cowboys postgame show on Fox Sports Net. As cautionary tales go, Ismail's could've been worse: He has his Notre Dame degree, and he never filed for bankruptcy, had legal trouble or got divorced. Yet he lost several million dollars, he admits, through "total ignorance."

It began in the winter of 1991 when he sank \$300,000 into the Rock N' Roll Café, a theme restaurant in New England designed to ride the wave of the Hard Rock Cafe and Planet Hollywood franchises. One of his advisers pitched the idea as "fail-proof, with no downsides," Ismail recalls. He never recouped his money and has no idea what became of the restaurant.

Lesson learned? If only. After that Ismail squandered a fortune funding not only that inspirational movie but also the music label COZ Records ("The guy was a real good talker," says Rocket); a cosmetics procedure whereby oxygen was absorbed into the skin ("We were not prepared for the sharks in the beauty industry"); a plan to create nationwide phone-card dispensers ("When I was in college, phone cards were a big deal"); and, recently, three shops dubbed It's in the Name, where tourists could buy framed calligraphy of names or proverbs of their choice ("The main store opened up in New Orleans, but doggone Hurricane Katrina came two months later"). The shops no longer exist.

You might say Ismail had a run of terrible luck, but the odds were never close to being in his favor. Industry experts estimate that only one in 30 of the highest-caliber private investment deals works out as advertised. "Chronic overallocation into real estate and bad private equity is the Number 1 problem [for athletes] in terms of a financial meltdown," Butowsky says. "And I've never seen more people come to me about raising money for those kinds of deals than athletes."

For the risk-averse investor, an adviser such as Butowsky would suggest allocating 5% to private equity, 7%-12% to real estate, 50%-65% to a mix of public securities (stocks, mutual funds and the like) and the rest to alternatives such as gold and hedge funds. Yet with athletes, who are often uninterested in either conservative spending or the stock market, those percentages are frequently flipped. Securities are invisible, after all, and if you don't study them, they're unintelligible. Not to mention boring. Inventions, nightclubs, car dealerships and T-shirt companies have an advantage: the thrill of tangibility.

Many players, consequently, are financial prey. "Disreputable people see athletes' money as very easy to get to," says Steven Baker, an agent who represents 20 NFL players. In May 2007 former quarterbacks Drew Bledsoe and Rick Mirer and five other NFL retirees invested at least \$100,000 apiece in a now-defunct start-up called Pay By Touch--which touted "biometric authentication" technology that would help replace credit cards with fingerprints--even as the company was wracked by lawsuits and internal dissent. (The players later sued the financial-services firm UBS, which had encouraged its clients to invest in Pay By Touch, for allegedly withholding information about the company founder's criminal history and drug use.)

About five years ago, Hunter says, he invested almost \$70,000 in an invention: an

inflatable raft that would sit under furniture. The pitch was that when high-rainfall areas were flooded, consumers could pump up the device, allowing a sofa to float and remain dry. "The guy I invested with came back and wanted me to put in more, about \$500,000," Hunter says. "Then I met [Butowsky], who just said, Hell no! I wound up never seeing that guy--or any of my money--again."

Hunter, who in November 2007 signed a five-year, \$90 million contract, has been able to absorb the loss. But innumerable other athletes have not been so lucky. Former (and perhaps future) NFL quarterback Michael Vick filed for Chapter 11 bankruptcy last July and recently put his mansion in suburban Atlanta on the market. That's partly because he is unable to repay about \$6 million in bank loans that he put toward a carrental franchise in Indiana, real estate in Canada and a wine shop in Georgia. "It's always so predictable," Butowsky says. "Everyone wants to be the next Magic Johnson"

But Johnson is the rare, luminous exception of tangibility gone right. In 1994 he started a chain of inner-city movie theaters and diligently built a business empire. Today Magic Johnson Enterprises includes partnerships with Starbucks, 24 Hour Fitness, Aetna and Best Buy, and its capital management division has invested over a billion dollars in urban communities.

The rule, unfortunately, is a mogul manqué like McAllister. According to a civil suit filed on Feb. 20 by Nissan, the running back owes the car company more than \$6.6 million plus almost \$300,000 in interest on his car dealership. Or Muhammad, whose Cleveland music company, Baylo Entertainment, is being sued by Wachovia for allegedly failing to pay back \$24,603.24 on a Visa Business Rewards credit card. Muhammad's 8,200-square-foot lakeside estate, which boasts a custom spa and the "largest residential aquarium in the Southeast," can now be had on eBay for \$1.95 million, \$800,000 less than he initially asked for.

"Without question, this recession is increasing the velocity of what's taking place with athletes," Butowsky says. "They're suffering tremendously." Retired NBA forward Vin Baker's seafood restaurant in Old Saybrook, Conn., was foreclosed on in February 2008 due to nearly \$900,000 in unpaid loans. (It has since reopened with help from an anonymous investor.) And former major league infielder Junior Spivey's portfolio of real estate has lately assumed the form of a sinkhole. "I'm taking a huge hit," says Spivey, who has been buying homes to sell and rent since 2001. (He won't say how many properties he owns.) "It's very tough, especially for someone like me who's not playing."

Then there are the unnamed athletes and team personnel who pawned 400 title rings to the online reseller championship-rings.net over the past three months, a spike of about 33% from the same period last year. (A 2008 Giants Super Bowl ring was among them.) "It's mostly younger players who've been selling," says Tim Robins, the site's owner. "It's the economy. Selling these items is always embarrassing, a last resort "

11.

Misplaced Trust

Salary aside, the closest analogue to a pro athlete is not a white-collar executive. It's a lottery winner--who's often in his early twenties. "With athletes, there's an extraordinary metamorphosis of financial challenge," says agent Leigh Steinberg, who has represented the NFL's No. 1 pick a record eight times. "Coming off college scholarships, they probably haven't even learned the basics of budgeting or keeping

receipts." Which then triggers two fatal mistakes: hiring the wrong people as advisers, and trusting them far too much.

"That's the killer," Magic Johnson says. Johnson started out by admitting he knew nothing about business and seeking counsel from the power brokers who sat courtside at the old L.A. Forum, men such as Hollywood agent Michael Ovitz and Sony Pictures CEO Peter Guber. Now, Johnson says, he gets calls from star players "every day"--Alex Rodriguez, Shaquille O'Neal, Dwyane Wade, Plaxico Burress---and cuts them short if they propose relying on friends and family. "It won't even be a conversation," says Johnson. "They hire these people not because of expertise but because they're friends. Well, they'll fail."

Says Hunter, "They'll say, 'I got this guy, a cousin who's an accountant.' But he's usually an accountant in the 'hood. You hire him, you're doing him a favor."

Strickland realized that all too late. In 2001, when a "friend of a close friend" of the nine-year NBA vet proposed a real-estate deal in Georgia, Strickland turned to his business manager: his dad, Matthew, a retired lieutenant colonel in the Air Force. The paperwork on the plot of land, which was on sale for \$1.8 million but supposedly had been appraised at as much as \$3 million, appeared legitimate, and Strickland bought it. "I trusted my father to help look it over for me because I was hooping and didn't have time," Erick says. "He checked it out. But he didn't go that extra length."

The land wasn't worth anything close to what Strickland was told. "I had to take that hit," he says. "I wish my dad hadn't been put in that position. He just didn't have the knowledge." As for his close friend? Strickland says the man secretly got a cut of the deal, and the conflict caused a permanent "falling out" between them.

Relatives are not the only ones foolishly trusted with athletes' money. One up-and-coming guard in the NBA allows his entire fortune to be managed by his former AAU coach, who has the player's power of attorney. In a meeting with Butowsky in December, the guard's dad admitted that he has no idea who the son's accountant is and said he wanted a financial "intervention."

The NBA player's ignorance of his own affairs is not unique. According to Bob Young, the managing director of Apex Wealth Management in Doylestown, Pa., "You'll say to a player, 'How are you doing?' A lot of the time they'll respond, 'I have no idea.' All the bills are paid by someone else, and none of the statements go to [the athlete]."

In fact, according to the NFL Players Association, at least 78 players lost a total of more than \$42 million between 1999 and 2002 because they trusted money to financial advisers with questionable backgrounds. In this rogues' gallery Robert Allen Stanford looks almost presidential--and shows that even when athletes trust financiers of high repute, things can go disastrously wrong. The dubious advisers included Luigi DiFonzo--a former felon who claimed he was an Italian count and defrauded players such as Hall of Fame running back Eric Dickerson before committing suicide in August 2000--and disgraced agent William (Tank) Black, who built a pyramid scheme that took a total of about \$15 million from at least a dozen players, including Patriots running back Fred Taylor.

Just last May, Atlanta hedge fund manager Kirk Wright was convicted on 47 counts of fraud and money laundering in a scheme involving more than \$150 million. His client list included at least eight NFL players; former safeties Blaine Bishop (who lost \$4 million, according to court documents) and Steve Atwater (who lost \$2.7 million) had recruited former Broncos stars Terrell Davis and Rod Smith to Wright's firm, unwittingly making them victims too. Soon after his conviction Wright committed

suicide in prison.

In October, Atwater himself received an investment pitch from a fellow athlete. Former quarterback Jeff Blake sent 102 other retired players an e-mail on behalf of Triton Financial, an investment firm in Austin, whose "athlete services" department Blake directs along with three other ex-QBs: Chris Weinke and the brothers Detmer, Ty and Koy. In the e-mail, a copy of which was obtained by SI, Blake claimed without caveat that "Triton is averaging 32% annualized return on its investments within the past five years."

Triton is an official partner of the Heisman Trophy Trust and the sponsor of the Triton Financial Classic, a PGA senior tour event. Its CEO, Kurt Barton, told SI that the firm manages "about \$300 million" in assets, and he claimed that Triton registered with the SEC (as is required by law of investment adviser firms with at least \$25 million in assets under management) "roughly six months ago, around October." But the Texas State Securities Board and Triton chief compliance officer David Tuckfield said that the company has not, in fact, done so. "Right now, we're only registered with Texas," Tuckfield said. "But we're passing the [assets] threshold, and we're confident that we'll need to file this year."

Says Paul Cohen, a real estate investor who owns properties in Austin, "In this economy, especially in real estate, anything you bought in the last two years is deeply underwater. I guess what [Triton is] saying could happen. But then again, I could target the moon with my rifle and shoot, but I ain't gonna hit it." (Barton did not dispute the email's 32% figure, but he and Tuckfield admitted to SI that Blake should not have sent it out. Barton also conceded that Triton was "not supposed to publish specific numbers about past performance" without significant disclaimers, including a disclosure of what the company had invested in.)

On a much smaller scale, Torii Hunter and Astros pitcher LaTroy Hawkins recall the story of a former major leaguer from the Dominican Republic whose adviser took care of all his financial matters. One day the player's mail came to the clubhouse and Hunter playfully asked to see it. "It turns out he was paying this guy \$5,000 a month on insurance for two cars in the Dominican Republic," Hunter says. "I got three cars, and I only pay \$250 a month. He'd been with and trusted this guy [for almost 18 years]!"

Advisers warn that such overcharging is the most common form of financial bloodletting for athletes. "It's basically large-scale shoplifting," Butowsky says. "Athletes don't know industry standards, so virtually every one of them is being robbed." Brokers will encourage them to buy bonds with longer maturities because the commissions on them are often larger. Or they'll overcharge on portfolios--2% or 3% instead of the customary 1%.

A few years ago, Butowsky recalls, he met with a former high-round NFL pick whose adviser, also a former player, said that he couldn't reveal how much he was charging to manage the athlete's tax-exempt municipal bonds "because of the Patriot Act." According to Butowsky, he was taking \$146,000 every year.

III.

Family Matters

In 1996, when Panthers owner Jerry Richardson--a former NFL flanker turned businessman--addressed his players, one of them asked, What's the most dangerous thing that could happen to us financially? "Without blinking an eye," Ismail recalls, "Mr. Richardson said, 'Divorce.' "

Players today would not disagree. In a survey reported by the financial-services firm Rothstein Kass in December, more than 80% of the 178 athletes polled--each with a minimum net worth of \$5 million and two thirds under the age of 30--said they were "concerned about being involved in unjust lawsuits and/or divorce proceedings." By common estimates among athletes and agents, the divorce rate for pro athletes ranges from 60% to 80%.

In divorce proceedings, of course, husbands routinely lose half of their net worth. But for athletes there is an aggravating factor: when the divorce happens. Most splits occur in retirement, when the player's peak earnings period is long over and making a comparable living is virtually impossible. Such timing is no accident. "There's this huge lifestyle change," says former NBA center Mark West, a licensed stockbroker who is now the Suns' vice president of player programs. "You and your wife are suddenly always at home, bugging each other. Before, you'd always say, 'I gotta go to practice.' Now you don't have to practice. You have to finish conversations."

Which often involve an incendiary subject: infidelity. "A friend of mine is a football player, and I asked him why he cheated on his wife," says Anita Hawkins, LaTroy's wife of 11 years. "He just said, 'I love her dearly, but I feel like I got married too early and didn't get to do what I wanted to do when I was young.'

Given all the pressures on a pro athlete's marriage, one safety valve might be the prenuptial agreement--something "very strongly" recommended by agent David Falk, who surged to prominence representing Michael Jordan (who did not have one). "The percentage of prenups amongst athletes is appreciably lower compared with nonathletes at the same economic level," says celebrity divorce lawyer Raoul Felder, who has represented the ex-wives of Patrick Ewing, Jason Kidd and Mike Tyson.

In 1994, when NBA center Dikembe Mutombo was engaged to Michelle Roberts, a med student, Roberts refused to sign a premarital contract the day before the wedding. Five hundred guests--including a large party from Mutombo's native Democratic Republic of Congo--had begun flying in to Washington. "[Roberts] never signed," Falk says, "and Mutombo never married the girl." Calling off the nuptials reportedly cost him \$250,000.

It's no coincidence that the woman a pro athlete often chooses to marry--and often at a young age--is his hometown sweetheart. For that reason he can't envision a ruinous divorce. "That was how you could tell if she really liked you, if she knew you before you made it," says West. But when a player does make it? "The question [for the athlete] becomes, When you get off the farm and see Paris, so to speak, can you really go back to the farm?"

Children almost always complicate the issue. How to limit paternity obligations is a challenge for pro athletes. Former NBA forward Shawn Kemp (who has at least seven children by six women) and, more recently, Travis Henry (nine by nine) have seen their fortunes sapped by monthly child-support payments in the tens of thousands of dollars. Last month Henry, who reportedly earned almost \$11 million over seven years in the NFL, tried and failed to temporarily reduce one of his nine child-support payments by arguing that he could no longer afford the \$3,000 every month. Two weeks later he was jailed for falling \$16,600 behind in payments for his child in Frostproof. Fla.

An aversion to family planning goes hand in hand with neglect of other forms of financial foresight, which can affect what happens to athletes' fortunes even after they die. Hall of Fame linebacker Derrick Thomas, who died at 33 following a January 2000 car crash, had ignored the urging of his financial adviser to make a will, and his

entire estate was left for the court to divide, touching off a legal battle among the five mothers of his seven children. (Of the estimated \$30 million Thomas had earned in the NFL, he had only \$1.16 million in valued assets at the time of his death.)

"Derrick didn't care about meeting with his planner, and we tried to set him up to do it 10 times," says Steinberg, who was his agent. "The sad truth is that there was a certain group of athletes who actually believed that if they ever sat down to write their wills, they were going to die."

IV.

Great Expectations

The thorniest question for a pro athlete, however, isn't how he handles himself and those closest to him. It's "how you handle the new people suddenly emerging in your life," says Richard Lapchick, director of the University of Central Florida's DeVos Sport Business Management program. "They'll be expecting help or money or jobs. Often players don't know how to say no."

It's all part of that ossified notion of how a pro athlete should live and provide for those around him. If he isn't consuming conspicuously, then he hasn't made it. "When I was a young buck," says Hawkins, "I was trying to spend all my money. Now I try to preach to young guys in the clubhouse who are like that. I've got all this stuff from 10 years ago--jewelry, rims--that I think, Why the f--- did I even buy this?"

Two years ago Rockets forward Ron Artest had a similar change of heart. He dismissed six friends who were involved with his record label and doing odd jobs for him while they lived in a house he was leasing for \$30,000 a year. This entourage's "level of helpfulness," said Artest's publicist, Heidi Buech, "was 50 percent." (The house they occupied had also been broken into while Artest was abroad.)

As soon as an athlete goes pro, people in search of handouts tend to stretch the definitions of family and friends. When Hunter went to his hometown of Pine Bluff, Ark., for his grandmother's funeral last August, he found Old St. James Baptist Church packed, the line of cars outside stretching for blocks. "But my grandma didn't know anybody," Hunter says. "She just lived at home." When he stepped outside the church, people "came running, all dressed up, chasing after me," Hunter says. "They were throwing CDs, projects, letters. . . . They were yelling, My sister's brother went to school with you!"

A different but equally potent pressure operates in the workplace--the clubhouse, the locker room and the team plane. "For rookies, it's like an unspoken initiation," says Strickland. "You're trying to get in good with the veterans, so you go beyond your means. You drive the nice car, splurge on a house."

The veterans don't mind giving explicit instructions. "I got ripped my first three years in the NFL, every day," says Tubbs. "I got on planes with a cassette player, and [a teammate] would tell me, 'They make CD players. You're in the NFL now.' "

Perhaps the upper limit on spending was set by the famously profligate Shaquille O'Neal, who--according to a document obtained by the Palm Beach Post during O'Neal's canceled divorce filing in January 2008--spends a total of \$875,015 each month, including \$26,500 for child care, \$24,300 for gas and \$17,220 for clothing. But O'Neal, who also has been known to fund charities anonymously and cover medical bills for complete strangers, has the wherewithal to remain solvent.

Imitators have been less fortunate. When former NBA guard Kenny Anderson filed for bankruptcy in October 2005, he detailed how the estimated \$60 million he earned in the league had dwindled to nothing. He bought eight cars and rang up monthly expenses of \$41,000, including outlays for child support, his mother's mortgage and his own five-bedroom house in Beverly Hills, Calif.--not to mention \$10,000 in what he dubbed "hanging-out money." He also regularly handed out \$3,000 to \$5,000 to friends and relatives. (Along with Ismail, he enlisted as both a Slamball coach and a Pros vs. Joes participant last year.) Former big league slugger Jack Clark filed for bankruptcy in July 1992 while still playing, listing debts of \$6.7 million and ownership of 18 cars--17 of which still had outstanding payments.

Financial advisers have come to call it "the problem of the \$20,000 Rolex." If a 22-year-old spends \$20,000 on a watch or on a big night out at a nightclub, that money is either depreciating or gone. "But if they invested in a five percent, Triple A insured, tax-free municipal bond for a period of 30 years," money manager Seymour says, "that \$20,000 would be worth \$86,000 at that tax-free rate of return. And needless to say, they buy more than one \$20,000 Rolex."

Four years ago future NBA Hall of Famer Scottie Pippen unsuccessfully sued his former law firm for allegedly losing \$27 million of his money through poor investments. (He had earned about \$110 million in salary alone over a 17-year career.) In February 2007--around the same time as Pippen's failed NBA comeback attempt--the Missouri Court of Appeals upheld a ruling that the player owed U.S. Bank more than \$5 million in principal, interest and attorneys' fees from a dispute regarding a Grumman Gulfstream II corporate jet that he'd purchased in 2001.

In an era in which banks are lambasted for using taxpayers' money to fly their executives on luxury private planes, it's a smart bet for players not to use their own cash to do the same. "In this economy, especially, the goal shouldn't be living that kind of lifestyle or trying to get richer," says West. "It needs to be about trying to maintain the wealth."

Sometimes, though, a jock just can't shake the temptation to try to hit the jackpot. Butowsky believes that "there's something in an athlete's mentality" that drives him to swing for the fences financially--usually at his own peril. "The solution to the problem is, without a doubt, education," the adviser says. "Change won't happen until grown men start wanting to learn."

Old habits die hard. Despite all his dreadful experiences, and lessons absorbed the hard way, not even Ismail is done yet. This time around, the project in which he's invested \$250,000 is a special mouth guard--available online for \$79.95--that's designed to help the body "physiologically perform at the highest level," he says. The science behind it involves relieving pressure on the temporomandibular joint and holding the jaw in an "optimal" position. (Ismail made the investment before he began consulting with Butowsky.)

It might sound familiar, Rocket admits, but there's at least one distinction between this and his previous six ventures: He didn't embark on it so blindly. He actually used the mouth guard during his playing career. He says he's close friends with the guy who designed it. ("He's my boy.") And, perhaps most important, Ismail saw the plan develop from the ground up.

Hours after Butowsky's boot camp in Dallas is over, Rocket calmly lays out his rationale: "You know that statistic we heard about how one in 30 private equity investments works?" He smiles broadly. "Well, Lord willing, this is going to be my

Somewhere heads are nodding.

EXHIBIT 66



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Former NFL Players: Disabilities, Benefits, and Related Issues

L. Elaine Halchin Congressional Research Service; Government and Finance Division

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Former NFL Players: Disabilities, Benefits, and Related Issues

Abstract

[Excerpt] Professional football is a very popular sport, and the physical nature of the game of football is part of its appeal, but, at the same time, playing the game can exact a physical and mental toll on players. Violent collisions, as well as other aspects of the sport, can and do cause injuries. Each week during the season, the National Football League (NFL) releases an injury report that lists, for each team, players who are injured, the type or location of the injury (for example, "concussion," "knee," or "ribs"), and the players' status for the upcoming game. During the 2007 season, aside from weeks one and eight, at least 10% of NFL players were identified each week as being injured. Players' injuries and current health conditions (for example, excess weight and sleep apnea) might have long-term consequences for their health, meaning that today's injury might become a chronic health problem or disability during retirement from the NFL. The issue has received considerable attention from Congress, including hearings in both chambers. Through collective bargaining agreement (CBA) negotiations and other discussions, the NFL and the NFL Players Association (NFLPA) have established a number of benefits, including retirement benefits (that is, a pension), severance pay, total and permanent disability benefits, and an annuity program. Some benefits are available to all players, while other benefits are available only to players who played in the NFL during certain years. Additionally, some benefits have eligibility requirements. Funds for benefits that are included in the CBA come from the portion of the league's total revenues that is allocated to the players. Apparently, the NFL and the NFLPA determine how to fund other benefits. The NFL and the NFLPA have taken steps to promote the health and safety of players. The league has established several committees, such as the Mild Traumatic Brain Injury (MTBI) Committee, and, through NFL Charities, awards grants for medical and scientific research related to health and safety issues. The NFLPA has a medical advisor and a performance consultant, and there is an NFL-NFLPA joint committee on player safety. The subject of injuries, disabilities, and benefits is a complex one, and there are a variety of issues surrounding this subject. For example, it has been argued that the way compensation is structured within the NFL might induce an individual to play while injured instead of seeking medical treatment. The oldest retired players might make up a subset with exceptional financial and medical needs, because they (1) might not have been protected as well as current players are; (2) might have received medical care that, while the best available at the time, was not as effective as the care available today; and (3) are not eligible for all of the benefits available to current players. Another issue involves MTBI research and whether multiple concussions might have long-term effects. The NFLPA proposed three legislative options in 2007. Other possibilities include establishing one or more ombudsman offices or taking steps to mitigate the economic risk of injuries and disabilities. This report will be updated as events warrant.

Keywords

professional football, National Football League, NFL, injury, disability, retirement, public policy, Congress, NFL Players Association, NFLPA

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CRS Report for Congress

Former NFL Players: Disabilities, Benefits, and Related Issues

April 8, 2008

L. Elaine Halchin Analyst in American National Government Government and Finance Division



Prepared for Members and Committees of Congress

Former NFL Players: Disabilities, Benefits, and Related Issues

Summary

Professional football is a very popular sport, and the physical nature of the game of football is part of its appeal, but, at the same time, playing the game can exact a physical and mental toll on players. Violent collisions, as well as other aspects of the sport, can and do cause injuries. Each week during the season, the National Football League (NFL) releases an injury report that lists, for each team, players who are injured, the type or location of the injury (for example, "concussion," "knee," or "ribs"), and the players' status for the upcoming game. During the 2007 season, aside from weeks one and eight, at least 10% of NFL players were identified each week as being injured. Players' injuries and current health conditions (for example, excess weight and sleep apnea) might have long-term consequences for their health, meaning that today's injury might become a chronic health problem or disability during retirement from the NFL. The issue has received considerable attention from Congress, including hearings in both chambers.

Through collective bargaining agreement (CBA) negotiations and other discussions, the NFL and the NFL Players Association (NFLPA) have established a number of benefits, including retirement benefits (that is, a pension), severance pay, total and permanent disability benefits, and an annuity program. Some benefits are available to all players, while other benefits are available only to players who played in the NFL during certain years. Additionally, some benefits have eligibility requirements. Funds for benefits that are included in the CBA come from the portion of the league's total revenues that is allocated to the players. Apparently, the NFL and the NFLPA determine how to fund other benefits.

The NFL and the NFLPA have taken steps to promote the health and safety of players. The league has established several committees, such as the Mild Traumatic Brain Injury (MTBI) Committee, and, through NFL Charities, awards grants for medical and scientific research related to health and safety issues. The NFLPA has a medical advisor and a performance consultant, and there is an NFL-NFLPA joint committee on player safety.

The subject of injuries, disabilities, and benefits is a complex one, and there are a variety of issues surrounding this subject. For example, it has been argued that the way compensation is structured within the NFL might induce an individual to play while injured instead of seeking medical treatment. The oldest retired players might make up a subset with exceptional financial and medical needs, because they (1) might not have been protected as well as current players are; (2) might have received medical care that, while the best available at the time, was not as effective as the care available today; and (3) are not eligible for all of the benefits available to current players. Another issue involves MTBI research and whether multiple concussions might have long-term effects. The NFLPA proposed three legislative options in 2007. Other possibilities include establishing one or more ombudsman offices or taking steps to mitigate the economic risk of injuries and disabilities. This report will be updated as events warrant.

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Former NFL Players: Disabilities, Benefits, and Related Issues

Introduction¹

Professional football, notably the National Football League (NFL), is the favorite sport of many in the United States.² Recognized by some as "America's most popular spectator sport," the NFL's "popularity has never been greater: in the past 20 years, football has sharply widened its lead over baseball as America's favorite professional sport, according to a Harris Poll in December [2005]. Fans choose football over baseball, basketball and auto racing combined...." The popularity of the sport also is reflected in the league's major television rights deals, which are summarized in **Table 1**.

Table 1. The NFL's Major Television Rights Contracts, 2006-2013

Network or Cable Channel	Years Covered by the Contract	Total Rights Fee	Average Annual Value		
CBS and Fox	2006-2011	\$8.0 billion	\$1.3 billion		
NBC	2006-2011	\$3.6 billion	\$600 million		
ESPN ^a	2006-2013	\$8.8 billion	\$1.1 billion		
Total		\$20.4 billion	\$3.0 billion		

Source: Sports Business Resource Guide & Fact Book, 2006 (Charlotte, NC: Street and Smith's Sports Group, 2005), p. E-120.

a. A comparable television rights deal between Major League Baseball and ESPN, for the period 2006-2013, has a total rights fee of \$2.37 billion and an average annual value of \$296 million. (*Sports Business Resource Guide and Fact Book*, 2006, 2005, p. E-120.)

Throughout the documents that govern retirement and disability benefits, "active" players are distinguished from inactive, or retired, players. In this context, "active" players generally are those under contract to a club or between teams; the

¹ This report was prepared at the request of the House Committee on the Judiciary.

² A list of acronyms used in this report may be found at **Appendix D**.

³ Hoover's, Inc., "National Football League," Dec. 11, 2007, available at [http://www.lexisnexis.com/]; and Steven Levingston, "NFL Plays Smash-Mouth Ball When It Comes to Branding," *Washington Post*, Feb. 5, 2006, p. A7.

term roughly corresponds to the bargaining unit under the CBA. The term "active player" also can arise in distinguishing among categories of players who are employed by teams. For example each team is permitted a maximum of 53 players on its roster for a game. This limited roster comprises an Active list, not exceeding 45, and an Inactive list. However, "active players," as used generally in this report extends beyond roster players those players employed while in other categories, injured reserve, for example.

Active and future players are represented by the NFL Players Association (NFLPA), which is the sole and exclusive bargaining representative for players.⁴ The average length of an NFL career is three and one-half seasons, and the average salary (which may include other types of compensation; see below for additional information) is \$1.1 million.⁵ Including both vested (i.e., having earned a sufficient number of "credited seasons" to qualify for retirement benefits) and nonvested players, the number of retired (or former) players is approximately 13,000. Vested players number approximately 7,900.⁶ Although, under the collective bargaining agreement (CBA), the NFLPA does not represent former players, it does negotiate with the NFL for benefits for retired players.⁷

Playing professional football can, for some individuals, exact a significant physical, and, in some cases, mental, toll. Yet, the excitement of big hits is part of the attraction of the sport. In 2003, ESPN introduced a segment, "Jacked Up," that featured the five biggest hits from the weekend's games, except for plays that

⁴ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, Mar. 8, 2006, p. 3. The term "future players" refers to individuals who had been previously employed by an NFL team and who are seeking employment with an NFL team; all rookie players, once they have been selected in the current year's draft; and all undrafted rookie players, once they begin negotiations with an NFL team. (Ibid.)

NFL Players Association, "FAQs: NFL Hopefuls FAQ," available at [http://www.nflpa.org/Faqs/NFL_HopefulsFaq.aspx] as of Jan. 14, 2008, on file with the author. The NFL Players Association established a new website in Mar. 2008, replacing the original url [http://www.nflpa.org], with this url: [http://www.nflplayers.com]. (NFL Players Association, "Ready, Set, Click! NFLPA to Launch New Website This Month," Mar. 6, 2008, available at [http://www.nflplayers.com/user/content.aspx?fmid=178&lmid=443&pid=310&type=n].) Following this change, some of the NFLPA documents obtained from the previous website apparently are no longer readily accessible at the new website. Citations for these documents include the date the author accessed and printed the relevant document. However, some of these documents are pdf documents, which means that the dates they were accessed via the previous NFLPA website do not appear on the document. The citations for this particular group of documents notes the month and year they were downloaded. Regarding documents obtained from the previous website that are accessible at the new website, the current url is provided.

⁶ Letter from Eugene Upshaw, Executive Director, NFL Players Association, to Reps. John Conyers, Jr., Lamar S. Smith, Linda T. Sanchez, and Christopher B. Cannon, Nov. 5, 2007, p. 8.

⁷ A Supreme Court ruling stated that "the ordinary meaning of 'employee' does not include retired workers...." (*Allied Chemical & Alkali Workers of America, Local Union No. 1 v. Pittsburgh Plate Glass Co., Chemical Division*, 404 U.S. 157 (1971), at 392.)

resulted in an injury or a penalty.⁸ Television news broadcasts often carry video replays of especially hard collisions. Some players achieve renown as "big hitters."

Despite the popularity of the physical nature of the game, it is balanced by concern for the players. One sports journalist has written of the game's violence, "Players live for it, fans love it, media celebrate it — and all bemoan its devastating consequences. The brutal collision of bodies is football's lifeblood, and the NFL's biggest concern."

For the purposes of this report, distinctions are made between injuries, disabilities classified as such under the Bert Bell/Pete Rozelle NFL Player Retirement Plan ("retirement plan"), disabilities generally, and chronic health problems. An injury is damage that occurs to an individual's body, in this case a professional football player, such as an abrasion, or a sprained ankle, torn muscle, or concussion. A retirement plan disability is a medical condition that qualifies as a disability under the NFL and NFLPA retirement plan. (See below for additional information about the different types of disabilities for which benefits are provided under the retirement plan.) The term "disability" also may be interpreted more broadly to include any inability or incapacity. Thus, a retired player who is incapable of performing one or more particular activities or functions, but does not receive any retirement plan disability benefits, also may be considered to be disabled. The phrase "chronic health problems" refers to conditions or illnesses that interfere with the activities of daily living, but do not rise to the level of rendering a player unable or incapable of performing an activity or function. For example, as reported by the Los Angeles Times in 2000, Joe Montana, former quarterback for the San Francisco 49ers, "does not qualify for disability payments ... [and appears] to be living a healthy, active postcareer life, [but he] suffers from an aching knee that makes [playing] golf painful, a numb foot that makes walking awkward and occasional blurred vision from too many hits to the head."11

Although the focus of this report is on former players, and their health problems and benefits, the report also covers certain issues involving active players. The health of retired players derives in part from the injuries and medical conditions (such as excessive weight, if not obesity) that they may have experienced during their playing days. Accordingly, some of the conditions, terms, or policies under which active players perform might have some bearing on their current and long-term health. The issue of former players and their health and benefits has received considerable attention from Congress, including hearings in both chambers.

⁸ Tim Layden, "The Big Hit," Sports Illustrated, July 30, 2007, p. 58.

⁹ Ibid., p. 53.

¹⁰ For example, a former player who is disabled but does not receive any disability benefits might not have applied for benefits; might not be eligible for disability benefits; might have applied and have his application pending; or might have applied, but had his application denied.

¹¹ Steve Springer, "After Care: Medical Benefits; Disability Payments Ease Pain; Unlike in Years Past, Former Players Who Are Totally and Permanently Disabled Receive Monetary Compensation," *Los Angeles Times*, Jan. 25, 2000, p. D8.

The next section describes the physical nature of the game of football, injuries, and health problems and is followed by a section on benefit programs and plans available to former players. After an overview of other organizations' efforts to aid former players, this report examines the NFL's and the NFL Players Association's health and safety initiatives, examines selected issues, and discusses possible courses of action.

The Game of Football and the Health of Players

Introduction

Comprehensive data about the health of former players apparently are not collected and maintained, either by the NFLPA or the NFL, or by a third party. The NFLPA is not aware of "any source of general data on the current health" of the 7,900 former players who are vested. ¹² Individual teams may have some information, but, apparently, the Retirement Plan Office does not. ¹³

Neither the players association nor the league collects data on number or percentage of players who retire because of an injury or injuries.¹⁴ The NFLPA notes:

[Players] may leave the game for several reasons. Statistics about why NFL players retire can be misleading. Most careers are not affected by a muscle or bone problem that causes a person to be one-half of a second slower in the 40-yard dash. In the NFL, that half-second could cost a player his job. The vast majority of players who leave the NFL, including those who leave because of injury, are in most respects quite healthy and capable of other employment.¹⁵

Although the last statement in this passage may be accurate, confirmation is difficult due to the dearth of evidence, and possibly some of the individuals who are "quite healthy" upon leaving the NFL might develop football-related disabilities later in life.

The NFL offers several possible reasons individuals retire from professional football: "Players retire for many reasons: because they do not make the team, because they wish to start their second career, because they lose the desire to play, or because they wish to spend more time with their families." Nevertheless, the NFL has some information on this subject which suggests that, for the period 1994-2004, at least 181 players retired for health reasons. This figure is 4% of the "4,362 players who earned a Credited Season" during the same period and who "appear to

¹² Letter from Upshaw to Reps. Convers, Smith, Sanchez, and Cannon, p. 8.

¹³ Ibid., p. 7. The Retirement Plan Office is responsible for administering the retirement plan which is part of the collective bargaining agreement.

¹⁴ Ibid., p. 13; Letter from Roger Goodell, Commissioner, National Football League, to Reps. John Conyers, Jr., and Lamar S. Smith, Nov. 2, 2007, p. 9.

¹⁵ Ibid.

¹⁶ Ibid.

have retired."¹⁷ The NFL was able to identify these 181 players because they received additional compensation after they "did not pass their pre-season physical[s] due to [injuries] sustained during the prior season and thus were unable to play." Not included in this count are players who decided to retire because of their injuries and thus did not submit to a pre-season physical.

Without comprehensive, complete, detailed, and accurate data, including the number and extent of all disabilities and chronic health problems, it is difficult to know the health status, or employment or financial status, of all former players, and not just those who already receive, in particular, disability benefits. As suggested above, some former players may have chronic health problems or may suffer from disabilities, as broadly construed, but do not receive any disability benefits from the retirement plan. The absence of information about this group of retirees makes it difficult to determine whether any of them do not receive sufficient assistance, and also might hamper efforts to determine the effects or consequences of football-related disabilities.

Despite the lack of data on the health of former players, however, descriptive information can provide some insight into the nature of professional football and football injuries, which, for some former players, might have long-term health consequences.

The Nature of the Game of Football

Physical contact is integral to the game of professional football. For some, though, the phrase "physical contact" is an inadequate description. Notably, Mike Ditka, a former player and coach in the NFL, stated, during a congressional hearing, that "[i]t is not a contact sport, it's a collision sport."¹⁹

Timothy Gay, a professor of physics at the University of Nebraska and author of *Football Physics: The Science of the Game*, asks,

What is the force of that hit? Well, you're talking about classical physics, which puts us in the province of Isaac Newton: Force equals mass times acceleration. What you come up with in this case is that each man exerts about 1,500 pounds of force, or three quarters of a ton, on the other. Which is why they call football a contact sport.²⁰

¹⁷ Letter from Goodell to Reps. Conyers and Smith, p. 9.

¹⁸ In some cases, an individual's health status and financial status may be related.

¹⁹ U.S. Congress, Senate Committee on Commerce, Science and Transportation, "Oversight of the NFL Retirement System," statement of Mike Ditka, unpublished hearing, 110th Cong., 1st sess., Sept. 18, 2007, p. 99.

²⁰ Layden, "The Big Hit," pp. 55-56. See also Timothy Gay, *Football Physics, The Science of the Game* (Emmaus, PA: Rodale Inc., 2004), pp. 35-36; and Gene Wojiechowski and Chris Dufresne, "Life Expectancy Low, Some Say: Football Career Is Taking Its Toll on NFL's Players," *Los Angeles Times*, June 26, 1988, available at [http://www.lexisnexis.com/].

At Virginia Polytechnic Institute and State University (Virginia Tech), a mechanical engineering professor put impact recorders in football players' helmets in 2003. The devices recorded 3,300 hits to the heads of players in 10 games and 25 practices. He also found that "[a] typical skull absorbed 50 wallops measured at 40 times the force of gravity...." Players collide during training camp, practice, pre-season, regular season and post-season games. Some players tear muscles and ligaments, break bones, and lose consciousness.

Each week during the season, the NFL releases an injury report that lists, for each team, players who are injured, the type or location of the injury (for example, "concussion," "knee," or "ribs"), and the injured player's status for the upcoming game (for example, "out," "questionable," or "probable"). Table 2 includes data for each week in the 2007 season. The data in this table may not provide an accurate count of the number of injuries sustained by NFL players for the following reasons:

(1) only one type of injury or injury location was listed on the report, but some players listed may have had more than one injury; (2) a player may not have reported his injury or injuries to his team's medical staff, and, hence, his name did not appear on the report; (3) a player may have reported his injury or injuries to the medical staff, but the type or severity of the injury or injuries did not preclude him from playing; and (4) a player whose injury status kept him from playing in games for more than one week could be listed on the injury report each week. More accurate injury data are submitted to the NFL's Injury Surveillance System (see below for additional information) by each team's medical staff.

²¹ Carl Prine, "Extra Pounds Cause Trouble Later in Life," *Pittsburgh Tribune-Review*, Jan. 9, 2005, available at [http://www.pittsburghlive.com/x/pittsburghtrib/news/specialreports/specialnfl/s_291051.html].

²² Carl Prine, "Bloody Sundays," *Pittsburgh Tribune-Review*, Jan. 9, 2005, available at [http://www.pittsburghlive.com/x/pittsburghtrib/news/specialreports/specialnfl/s_291033.html].

²³ Peter Carlson, "For the NFL's Retirees: Know Pain, No Gain," *Washington Post*, Aug. 21, 2007, p. C7; and Paul Gutierrez, "NFL Injuries; Pain Game," *Los Angeles Times*, Jan. 25, 2000, available at [http://www.lexisnexis.com/].

²⁴ According to a news article, "The [NFL's] injury lists have roots in two mandates: State workers' compensation laws and federal reporting requirements force teams to record injuries. Because a paper trail is needed to substantiate a potential on-the-job disability or safety issue, broken bones, joint tears, ruptured muscles, head wounds and other ailments are written down. NFL bylaws also require teams disclose to their opponents their players' pre-game injury status so coaches can prepare strategies." (Prine, "Bloody Sundays.") Regarding an injured player's status, Prine reported that "even a player marked 'probable' for Sunday's game has a 'serious' injury, much as a bad fall or a degenerative bone condition would be considered serious on a workers' compensation filing. 'As a fan, maybe you don't think it's serious because the player is playing, but [the injury] can still be serious,' said Dr. Derek Jones, one of the nation's foremost orthopedic surgeons at the Ochnser Clinic in New Orleans." (Ibid.)

Table 2. Number of Players Listed on the NFL's Injury Report, 2007 Season

Week During the Season	Number of Players ^a	Percentage of Players ^b
1	132	8%
2	167	10%
3	202	12%
4	208	12%
5	207	12%
6	179	11%
7	190	11%
8	159	9%
9	188	11%
10	185	11%
11	195	11%
12	181	11%
13	198	12%
14	211	12%
15	207	12%
16	203	12%
17	216	13%

Source: National Football League, "Injuries," available at [http://www.nfl.com/injuries].

Aside from weeks one and eight, at least 10% of NFL players are identified each week as being injured. The relatively small variation in the percentage of players identified as being injured each week throughout a 17-game season — 10% to13% — suggests, despite questions about the accuracy of the data, that a fairly consistent number of players are injured throughout the season.

A journalist for the *Pittsburgh Tribune-Review* conducted an analysis of four years of data culled from the NFL's weekly injury reports, interviewed 200 current and former players, coaches, and managers about injuries, and reviewed medical literature. A summary of his findings is as follows:

a. These figures do not include any player who was listed on a team's injury report, but for whom the entry in the "Injury" column was "Appendicitis," "Coach's Decision," "Migraine," "Personal," "Personal Decision," "Personal Reason," "Team decision," or "Illness."

b. Percentages have been rounded.

In the 2000 through the 2003 seasons, NFL players racked up 6,558 injuries. More than half the athletes are hurt annually, with the number spiking at 68% in 2003-04, according to the NFL's weekly injury reports.

Defenders are injured more than their foes on the offense. A defensive back alone is 30 percent more likely to get hurt than a quarterback, even though a passer touches the ball on every possession. Two out of three cornerbacks and safeties suffer injuries in the NFL annually, and half of those will suffer a second, unrelated injury before the Super Bowl.

Quarterbacks, tight ends, wide receivers, safeties and cornerbacks routinely suffer high rates of brain concussions and spine injuries that could trigger paralysis, dementia, depression and other ailments later in life. During typical four-year careers, one of every 10 NFL receivers experiences a concussion. On average, seven pro football players a week face potentially life-altering head, spine or neck trauma.²⁵

Additionally, the news article noted that, during the four-year period studied, 1,205 players had knee injuries; 652 sustained head, spine, or neck trauma; 683 injured their hamstring and groin muscles; and 928 broke or sprained their ankles. Reportedly, the "2003 NFL injury rate was nearly eight times higher than that of any other commercial sports league, according to the U.S. Department of Labor — and that includes the National Hockey League, the National Basketball Association, and professional auto racing." 27

Another newspaper, the *Los Angeles Times*, also used the NFL's weekly injury reports to compile data for several seasons, 1997-1999. In 1997, 335 players were sidelined for 937 games; in 1998, 398 players sat out 1,340 games; and, in 1999, 364 players did not play in 1,061 games.²⁸ **Table 3** shows the types of injuries sustained by NFL players for these three years. The data in this table are not comparable to the data provided in **Table 2**. A key difference between the two datasets is that the *Los Angeles Times* researcher who compiled the data found in **Table 3** tracked individual players.²⁹ Nevertheless, some of the same caveats that apply to **Table 2** also might apply to **Table 3**. That is, the data in **Table 3** may not provide an accurate count of the number of injuries sustained by NFL players for the following reasons: (1) only one type of injury or injury location was listed on the report, but some players listed may have had more than one injury; (2) a player may not have reported his injury or

²⁵ Prine, "Bloody Sundays."

²⁶ Ibid.

²⁷ Ibid.

²⁸ Gutierrez, "NFL Injuries; Pain Game."

²⁹ Specifically, he "tracked every player who suffered an injury during the 1997, '98, and '99 seasons. Those players who were sidelined for a game or more because of injury were logged, as were the number of games they were sidelined and the types of injuries. Players who were injured in the previous season or in the exhibition season and missed games the next season ... were not counted." (Houston Mitchell, "NFL Injuries; Injury Report; Methodology," *Los Angeles Times*, Jan. 25, 2000, available at [http://www.lexisnexis.com/].)

injuries to his team's medical staff and hence his name did not appear on the report; (3) a player may have reported his injury or injuries to the medical's staff, but the type or severity of the injury or injuries did not preclude him from playing.

Table 3. NFL Players' Injuries by Type of Injury, 1997-1999

Type of Injury or Illness	1997ª	1998ª	1999ª
Abdomen	2 1%	6 1%	1 <1%
Abrasions	0	0	1 <1%
Achilles tendon	3 1%	3 1%	5 1%
Ankle	50 14%	54 13%	52 14%
Arm	5 1%	5 1%	4 1%
Back	12 3%	23 5%	9 2%
Biceps	0	4 1%	1 <1%
Blood clot	0	0	1 <1%
Buttocks	1 <1%	0	0
Calf	4 1%	10 2%	7 2%
Chest	0	5 1%	2 1%
Concussion	5 1%	5 1%	11 3%
Elbow	7 2%	4 1%	5 1%
Ear	1 <1%	0	0
Eye	3 1%	2 <1%	0
Face laceration	0	0	1 <1%

Type of Injury or Illness	1997ª	1998ª	1999ª
Finger	1	4	1
	<1%	1%	<1%
Foot	8	23	19
	2%	5%	5%
Groin	12	14	10
	3%	3%	3%
Hamstring	29	35	30
	8%	8%	8%
Hand	12	9	2
	3%	2%	1%
Head	3	2	1
	1%	<1%	<1%
Heel	1 <1%	0	0
Hernia	1 <1%	0	1 <1%
Hip	6	2	4
	2%	<1%	1%
Jaw	2	2	1
	1%	<1%	<1%
Kidney	0	1 <1%	0
Knee	104	131	122
	30%	31%	33%
Leg	14	7	7
	4%	2%	2%
Liver	0	0	1 <1%
Neck	11	13	14
	3%	3%	4%
Nose	1 <1%	0	0
Pelvis	1 <1%	0	0
Quadriceps	3	2	7
	1%	<1%	2%

CRS-11

Type of Injury or Illness	1997ª	1998°	1999°
Ribs	6 2%	4 1%	4 1%
Shin	0	1 <1%	0
Shoulder	22 6%	35 8%	31 8%
Thigh	3 1%	1 <1%	0
Throat	0	0	1 <1%
Thumb	5 1%	4 1%	4 1%
Toe	5 1%	3 1%	6 2%
Triceps	1 <1%	2 <1%	1 <1%
Wrist	3 1%	3 1%	0
Total	347	419	367

Source: Houston Mitchell, "NFL Injuries; Injury Report; Methodology," *Los Angeles Times*, Jan. 25, 2000, available at [http://www.lexisnexis.com/].

a. Percentages have been rounded.

According to **Table 3**, players sustained 43 different types of injuries. Four types of injuries accounted for 50% of the injuries in each year: knee, ankle, hamstring, and shoulder. The breakdown for each of these injuries, by year, is as follows:

Knee: 30%, 31%, and 33%
Ankle: 14%, 13%, and 14%
Hamstring: 8% each year
Shoulder: 6%, 8%, and 8%

Given the focus on mild traumatic brain injury (MTBI, or concussions) in 2007, and the related anecdotal evidence on the frequency of concussions, it is notable that only 21 concussions were recorded for this three-year period (1997-1999). Concussions accounted for 1% of injuries in 1997 and in 1998, and 3% in 1999.

For some players, the injuries they sustain playing in the NFL might lead to disabilities later in life. David Meggyesy, a former player and the director of NFLPA's San Francisco office, reportedly referred to post-NFL injuries as "the

elephant in the room that no one wants to say is in the room.... Everybody walks away with an injury.... You just don't see that being done to the human body and not think there are going to be consequences later in life." Echoing Meggyesy's comments, a former president of the NFLPA, Trace Armstrong, offered his observations of other former players: "You go to our retired players' conventions ... and some of these guys don't look so good. Young men, onetime great athletes, but they don't move around so well."

Health Problems

Although accurate, complete, comprehensive, and detailed data about former and active players are necessary to construct a comprehensive picture of their health, the following information is useful for illustrating some of the health problems football players might experience, whether as active players or as retirees.

An obvious feature of most football players is their size. From 1985 through 2005, the average weight of a player in the NFL grew by 10% to an average of 248 pounds. At the heaviest position, offensive tackle, the average weight of players has increased from 281 pounds in the mid-1980s to 318 pounds in 2005.³¹ As of 2005, 552 players weighed 300 pounds or more, which is 33% of all active players, and 82 other players weighed between 295 and 299 pounds.³²

Not only are football players large, but some of them also may be classified as obese. Joyce B. Harp and Lindsay Hecht calculated the body mass index (BMI) of NFL players active during the 2003-2004 season and reported these findings:³³

- 97% of the players had a BMI of 25 or greater.
- 56% had a BMI of 30 or greater. This was 32 percentage points higher than the percentage of 20- to 39-year-old men who had comparable BMIs in the 1999-2002 National Health and Nutrition Examination Survey (NHANES).³⁴
- 26% of the players had a BMI of 35 or greater.

³⁰ David Steele, "Adding Insult to Injury," *San Francisco Chronicle*, Sept. 1, 2002, available at [http://sfgate.com].

³¹ Thomas Hargrove, "Heavy NFL Players Twice as Likely to Die Before 50," *Espn.com*, Jan. 31, 2006, available at [http://sports.espn.go.com/nfl/news/story?id=2313476].

³² Mark Maske and Leonard Shapiro, "NFL Is Soul Searching After Herrion's Death," *Washington Post*, Aug. 25, 2005, p. E8.

³³ For this study, "body mass index (BMI) was calculated for each of the players as weight in kilograms divided by height in meters squared, as was mean BMI for each team and position across all 32 teams and a frequency distribution of BMI for all players." (Joyce B. Harp and Lindsay Hecht, "Obesity in the National Football League," *Journal of the American Medical Association*, vol. 293, no. 9, Mar. 2, 2005, p. 1061.)

³⁴ Information about the National Health and Nutrition Examination Survey is available at [http://www.cdc.gov/nchs/nhanes.htm].

- 3% of the players had a BMI of 40 or greater. This percentage was similar to the percentage (3.7%) of 20- to 39-year-old men who had comparable BMIs in the 1999-2002 NHANES.
- Cornerbacks and defensive backs had the lowest mean BMI (26.8).
- Guards had the highest mean BMI (38.2).³⁵

In this study, "body mass index was classified according to the National Institutes of Health guideline: normal weight (BMI 18.5-24.9), overweight (25-29.9), obese class 1 (30-34.9), obese class 2 (35-39.9), and obese class 3 (\geq 40)." These data show that slightly more than half of the players were obese, with 26% having a BMI that "qualifie[s] as class 2 obesity." The authors concluded their article with the following comment:

Although measurements of body composition are needed to determine the source of the increased weight, it is unlikely that the high BMI in this group, particularly in the class 2 obesity range, is due to a healthy increase in muscle mass alone. The high number of large players was not unexpected given the pressures of professional athletes to increase their mass. However, it may not be without health consequences. A recent study described increased sleep-disordered breathing in professional football players, particularly those with a high BMI; linemen, who had the highest BMIs, also had higher blood pressures than did other players. The high prevalence of obesity in this group warrants further investigation to determine the short- and long-term health consequences of excessive weight in professional as well as amateur athletes.³⁸

Dr. Elliott Pellman, former medical advisor/liaison to the NFL Commissioner, reportedly critiqued the Harp and Hecht article by saying: "'[The BMI] is okay if you're an actuary for life insurance.... But medically, we don't define obesity that way. It's not designed for people that large. The study the [NFL] commissioner ordered will do a lot more than take heights and weights off the Internet. The data must be gathered in a scientific way."³⁹

³⁵ Harp and Hecht, "Obesity in the National Football League," pp. 1061-1062.

³⁶ Ibid., p. 1061.

³⁷ Ibid., p. 1062.

³⁸ Ibid., p. 1062.

³⁹ Maske and Shapiro, "NFL Is Soul Searching After Herrion's Death," p. E8. It is unclear whether the subject of obesity will be part of the NFL's study on cardiovascular health, or it will be the subject of a separate study. See **Appendix B** for a list of planned or ongoing studies. Elliot Pellman was medical advisor/liaison to the NFL Commissioner for the period 2001-2006. (Elliot J. Pellman, "Curriculum Vitae," provided by the House Committee on the Judiciary to the author on Nov. 6, 2007, p. 3.) Dr. Pellman served as the Chairman of the NFL Committee on Mild Traumatic Brain Injury (MTBI) from 1994 through 2007. His residencies and fellowship were in the fields of internal medicine and rheumatology. He continues to serve on the MTBI Committee, and he also serves on the Alliance for NFL Retired Football Players (member, 2007-present), the NFL's Foot and Ankle Committee (advisor, 2005-present) and Cardiovascular Health Committee (advisor, 2004-present), the NFL-NFLPA Joint Committee on Player Safety (member, 2001-present), the NFL's Injury and Safety Panel (advisor, 1995-present). Previously, he served as a member of the National (continued...)

Reportedly, some NFL linemen have a provision in their contracts saying they agree to maintain their size.⁴⁰ In Article XXIV, Section 7(c) of the CBA, which addresses financial incentives in players' contracts, examples of incentives that are considered "within the sole control of the player" include "weight bonuses."⁴¹ "Weight bonuses" is open to interpretation. For example, a player may be required to not exceed a certain weight or not to fall below a certain weight. Reportedly, Gene Upshaw, executive director of the NFLPA, said, in 2002, that the players association and the league had been discussing "how to deal with weight-loss demands by coaches. Is science involved? What factors do height and weight play? How long does it take the player to lose it?"⁴² It is unclear, though, whether this reference to weight loss is related to the possibility of a weight contract clause.

Obesity itself, plus simply being overweight, can lead to other health problems, both indirectly and directly. Players who have retired from the NFL may have difficulty decreasing their weight and staying in shape, particularly if they suffer from other health problems that preclude or limit their physical activity. Kevin Guskiewicz, research director of the Center for the Study of Retired Athletes (CSRA), University of North Carolina at Chapel Hill, as quoted in the *New York Times*, adds pain to the equation and describes a possible chain of events for former players: "What happens is that the retired athlete can't exercise because of the injuries he's sustained and the pain he is in, and that leads to higher weight, depression, bad eating habits, high blood pressure and so on."

Sleep apnea and cardiovascular disease (CVD) are examples of two health problems associated with excess weight. A 2003 study by SleepTech Consulting Group found that 34% of offensive linemen suffered from sleep apnea. As reported by the *New York Times*, an associate team physician with the New York Giants, Dr. Allan Levy, describes what some NFL players might experience:

The problem with sleep apnea is in the neck. A 17 ½-inch neck is usually where the problem begins. When they sleep, the muscles relax in the body. Now the

Football League Physicians Society's executive committee, from 1994 through 2003. (Ibid., pp. 1-5.)

³⁹ (...continued)

⁴⁰ Prine, "Extra Pounds Cause Trouble Later in Life."

⁴¹ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 109.

 $^{^{42}}$ Thomas George, "Care by Team Doctors Raises Conflict Issue," July 28, 2002, available a t $\,$ [h t t p : // q u e r y . n y t i m e s . c o m / g s t / f u l l p a g e . h t m l ? r e s = 990DEFDE173BF93BA15754C0A9649C8B63].

⁴³ Ibid.

⁴⁴ Harvey Araton, "Stealth Killer Puts Doctor on Mission with N.F.L.," *New York Times*, May 8, 2007, available at [http://query.nytimes.com/gst/fullpage.html?res=9C02EED71631F93BA35756C0A9619C8B63&n=Top/News/Sports/Columns/Harvey% 20Araton]. Information about the Center for the Study of Retired Athletes may be found at [http://www.csra.unc.edu/index.htm].

⁴⁵ Prine, "Extra Pounds Cause Trouble Later in Life."

weight of their neck clasps down on their airway. They stop breathing. They momentarily wake up, then the cycle starts over again, and they never get into deep sleep. They develop heart disease and hypertension. Sleep apnea is a killer. One of the kids that played for us, we did a sleep study on [him], [he] had 440 awakenings during the night.⁴⁶

Dr. Arthur Roberts, a cardiac surgeon who played in the NFL for three years, summarized the cardiovascular risk for professional football players. His summary, which was included in a *Washington Post* news article, follows:

The real problem is what's happening inside these men to their cardiovascular risk factors. The combination of large body size is associated with increased risk factors for diabetes and hypertension, which lead to so many other problems. Doctors have learned over the last 30 years that so many bad outcomes are related to cardiovascular problems that might have been avoided Cardiac arrest in the locker room is tragic but, thank God, a rare event But many of the risk factors that are in these players' bodies are not apparent now but will be apparent later in life. We have to shift the pendulum and evaluate and educate the younger players, make it a total process. With retired players we're finding high cholesterol and high blood pressure. We already know sleep apnea is associated with heart arrhythmia and hypertension. You have a lot of risk factors building in players. We have to make them aware and start educating them on how to take care of themselves to avoid problems later on. We have the technology to do it. We have a support system of doctors and hospitals involved in this study willing to do it. It's now a matter of getting players to buy into it.⁴⁷

Roberts was referring to a study of past and present players involving, among other things, the consequences of excess weight for cardiovascular health.⁴⁸ In contrast, a study designed to assess whether there is a link between playing professional football and reduced risk later in life for CVD, osteoporosis, and higher muscle mass reached an encouraging conclusion:

In this small [16 former NFL players] sample of older men, former successful professional athletes who remained physically active in middle age have a favorable body composition and reduced risk factors for CVD and osteoporosis compared with health age-and BMI-matched older men.⁴⁹

The findings of this study do not necessarily contradict Kevin Guskiewicz's comment above. This study included former players "who remained physically active in

⁴⁶ Clifton Brown, "Ex-Players Dealing With Not-So-Glamorous Health Issues," *New York Times*, Feb. 1, 2007, available at [http://query.nytimes.com/gst/fullpage.html?res=9D0CEFDB153FF932A35751C0A9619C8B63&n=Top/Reference/Times%20Topics/People/B/Brown,%20Clifton].

⁴⁷ Maske and Shapiro, "NFL Is Soul Searching After Herrion's Death," p. E8.

⁴⁸ Ibid.

⁴⁹ Nicole A. Lynch, Alice S. Ryan, Joyce Evans, Leslie I. Katzel, and Andrew P. Goldberg, "Older Elite Football Players Have Reduced Cardiac and Osteoporosis Risk Factors," *Medicine & Science in Sports & Exercise*, 2007, p. 1124.

middle age," while Guskiewicz was referring to retired players who are unable to exercise because of injuries sustained during their NFL careers.

Responding to a request from the NFLPA, the National Institute for Occupational and Safety and Health (NIOSH) conducted a mortality study in the early 1990s of the rate and causes of death of NFL players.⁵⁰ The study found the following:

- Former offensive and defensive linemen "had a 50% greater risk of cardiovascular disease than the general population."⁵¹
- Linemen "had a 3.7 times greater risk of cardiovascular disease" than players in other positions.⁵²

Possibly lending credence to questions about the size of players, the authors noted that "[i]t is not possible from this analysis to determine specifically what it is about the linemen, besides BMI, that contributes to this increased risk."⁵³

As described above, players sustain hits to the head, which may or may not result in a mild traumatic brain injury (MTBI) or concussion. Reportedly, league data show that approximately 100 players a year sustain concussions.⁵⁴ (For more information on MTBI, see below, in the "Discussion of Selected Issues" section.)

A study that focused on the long-term effect of concussions, however, also reported information about other health problems experienced by former players. The researchers found, by questioning 2,488 former NFL players, that 22% had knee surgery and 10% had back or disc surgery after their careers ended. In response, the NFL's medical advisor/liaison reportedly said that there is little credible research on whether playing football leads to serious medical problems later in life.

⁵⁰ A January 2006 news article reported that Dr. Sherry Baron, co-author of the 1994 study, was planning to repeat her study of mortality rates within the NFL. (Thomas Hargrove, "Compared to Baseball, Football Players Die Younger," *Espn.com*, Jan. 31, 2006, available at [http://sports.espn.go.com/nfl/news/story?id=2313520].) The status of the planned study is not known.

⁵¹ Letter from Sherry Baron, M.D., M.P.H., and Robert Rinsky, U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, to Frank Woschitz, National Football League Players Association, Jan. 10, 1994, p. 4. This letter is popularly known as the "NFL mortality study."

⁵² Ibid., p. 4.

⁵³ Ibid., p. 4.

Peter Keating, "Doctor Yes," *ESPN.com*, Oct. 28, 2006, available at [http://sports.espn.go.com/espn/print?id=2636795 &type=story].

⁵⁵ Ellen E. Schultz, "A Hobbled Star Battles the NFL," *Wall Street Journal*, Dec. 3, 2005, p. A2.

⁵⁶ Ibid., pp. A2-A3.

A study of depression and pain experienced by former NFL players also surveyed them about the most common problems they experience in retirement. The results, "in descending order of frequency as quite or very common" were: "difficulty with pain (48%), loss of fitness and lack of exercise (29%), weight gain (28%), trouble sleeping (28%), difficulty with aging (27%), and trouble with transition to life after professional football (27%)." Regarding the thrust of the study, the study's authors wrote:

Although pain and depression are commonly comorbid in the general population ..., the frequency with which retired professional football players report difficulty with pain seems to put them at additional risk of both developing depression and experiencing associated difficulties with retirement. The high level of psychosocial dysfunction and significant barriers to receiving help put a small but important subgroup of all retired NFL players at significant risk of adverse life events and disability, almost certainly including an increased risk of suicide.... Retired professional football players experience depressive symptoms at a rate that is similar to that found in the general population, presumably with a corresponding rate of clinical depression. They bear an additional burden of substantial chronic pain. Depressive symptoms and pain interact to result in a strong correlation with self-report perceptions of the risk of sleeping problems, difficulty with aging, loss of fitness and lack of exercise, financial problems, and concerns about their use of prescription and recreational drugs and alcohol.⁵⁸

What, if any, relationship exists between playing professional football and mortality is unclear. The 1994 NIOSH study mentioned above found that professional football players had "a 46% lower overall mortality rate than the general United States male population with a similar age and race distribution." A review of data on the mortality of those who played football, and those who played baseball, a sport with less physical contact. Deceased players from both sports born before 1955" were about equally likely to suffer an early death." However, differences between these two groups of athletes did appear for players born after 1955.

- At least 130 of the 8,961 football players and 31 of the 4,382 baseball players born after 1955 are known to have died. That is, 1 in every 69 football players and 1 in every 154 baseball players born after 1955 have died.
- The most common cause of death for baseball players was accidents; only one-third died of medical causes. Over half (52%) of the deceased football players "succumbed to conditions such as coronary

⁵⁷ Thomas L. Schwenk, Daniel W. Gorenflo, Richard R. Dopp, and Eric Hipple, "Depression and Pain in Retired Professional Football Players," *Medicine & Science in Sports and Exercise*, 2007, pp. 600-601.

⁵⁸ Ibid., pp. 603-604.

⁵⁹ Letter from Baron and Rinsky to Woschitz, p. 4.

⁶⁰ Thomas Hargrove, "Compared to Baseball, Football Players Die Younger."

disease, stroke and cancer — diseases known to be more common among obese people."⁶¹

• "The deceased baseball players averaged 192 pounds during their athletic careers while the dead football players averaged 238 pounds. Football players who died of medical causes averaged 248 pounds." 62

Complete, detailed, comprehensive, and accurate data are needed to construct a profile of the health of active players and former players. Furthermore, this type of initiative potentially could facilitate efforts to determine what links exist, if any, between injuries sustained as an active player and chronic health problems and disabilities (as broadly construed) experienced as a retired player.

NFL and NFLPA Benefit Programs and Plans

History of Benefits

Both the league and the players association are involved in the funding and provision of benefits to former players as well as active players. Most of the benefits for former players are administered by joint boards "to which the NFLPA and the NFL each appoint three voting members. The day-to-day administration of these jointly-trusteed benefits occurs at the 'Plan Office' in Baltimore" That is, neither the NFLPA nor the NFL administers certain benefits, such as the benefits included in the retirement plan, although the NFL is the sole administrator for severance pay and post-career health insurance. 63

Although the name and composition of the league has changed over the years, the league was formed in 1920, and adopted its current name in 1922.⁶⁴ The NFL Players Association was founded a number of years later, in 1956.

The following history of selected events shows the evolution of benefits for NFL players. Events that are not directly related to the establishment or enhancement of benefits are included to provide context or background information. Such events may include strikes, lockouts, and lawsuits, which are included for the period 1987-1993, when several events and decisions culminated in significant changes in benefits. However, since this is not a history of labor relations between the league and the players association, the chronology does not necessarily include all of the labor-management issues or milestones.

⁶¹ Ibid.

⁶² Ibid.

⁶³ Ibid., p. 29.

⁶⁴ The NFL as it exists today was created through a merger in 1966 with another league, the American Football League, which was formed in 1959.

- 1958. Team owners created "a benefit plan that included hospitalization, [and] medical and life insurance with a plan for retirement benefits at age 65." 65
- 1960s. "Players pushed through pension coverage [for] a group of 110 players who were in the league in 1959, when benefits were introduced. Life insurance and health coverage benefits were improved and, for the first time, two player reps [representatives] were designated to sit on the Retirement Board."66
- 1962. The NFLPA obtained the first pension agreement, known as the Bert Bell NFL Player Retirement Plan. The plan does not include players who left the game before 1959 (known as the "pre-59ers").⁶⁷
- 1966. The Commissioner of the NFL announced that the NFL and American Football League (AFL) will merge into one league.
- 1968. The NFLPA, which represented players on only 16 of the 26 teams (the AFL Players Association represented players on the remaining 10 teams), "proposed new pension demands" A lockout is followed by a brief strike, and eventually the parties agreed to what was the first CBA, which was effective from July 15, 1968, through February 1, 1970. Negotiations resulted in "a minimum salary of \$12,000, better pay for exhibitions, and a doubling of the annual pension-fund contribution to \$3 million." The NFLPA demands included a retirement age of 45; but, the retirement age in the CBA was set at age 65.
- 1970. The AFL Players Association and the NFL Players Association merged and retained the latter's name. The NFLPA was

⁶⁵ NFL Players Association, "About Us: NFLPA History," n.d., available at [http://www.nflpa.org/AboutUs/NFLPA_History.aspx] as of Oct. 2, 2007, on file with the author.

⁶⁶ Ibid.

 $^{^{67}}$ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," n.d., available at [http://nflpa.org/pdfs/NewsAndEvents/History_of_the_NFLPA%E2%80%99s_Retired_Player_Benefits.pdf], downloaded Sept. 2007, on file with the author.

⁶⁸ NFL Players Association, "About Us: NFLPA History"; *The Business of Football 2001* (Carmel, CA: Paul Kagan Associates, Inc., 2001), p. 392.

⁶⁹ Stephen Fox, *Big Leagues, Professional Baseball, Football, and Basketball in National Memory* (Lincoln, NE: University of Nebraska Press, 1994), p. 425.

⁷⁰ The Business of Football 2001, p. 393.

certified as a union.⁷¹ The American Football League (AFL) and the NFL merged and retained the latter's name. "The Players Negotiating Committee and the NFL Players Association announced a four-year agreement guaranteeing approximately \$4,535,000 annually to player pension and insurance benefits.... The owners also agreed to contribute \$250,000 annually to improve or implement items such as disability payments, widows' benefits, maternity benefits, and dental benefits." Players also were given the "right to meaningful representation on the Retirement Board, and the right to impartial arbitration of injury grievances." Total and permanent (T&P) disability benefits and line-of-duty (LOD) disability benefits were established. The pension plan was revised and set up in its present structure. Monthly pension is based on the number of years an individual plays football, not on the amount of his salary.

- 1973. A nonprofit organization, NFL Charities, was created "to support education and charitable activities and to supply economic support to persons formerly associated with professional football who were no longer able to support themselves."⁷⁶
- 1974-1976. NFL and NFLPA played three seasons without a CBA.⁷⁷
- 1977. The NFL Management Council and the NFLPA ratified a CBA which continued "the pension plan including years 1974, 1975, and 1976 with contributions totaling more than \$55 million.... The agreement ... reduced pension vesting to four years ... [and] improved insurance, medical, and dental benefits." Specifically, Group Insurance was established. Players were permitted to get a lump sum "early payment benefit" from their pension; the lump sum equaled 25% of their pension.

⁷¹ NFL Players Association, "About Us: NFLPA History."

⁷² National Football League, "History, 1961-1970," n.d., available at [http://www.nfl.com/history/chronology/1961-1970].

⁷³ NFL Players Association, "About Us: NFLPA History."

⁷⁴ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 4.

⁷⁵ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players."

⁷⁶ National Football League, "History, 1971-1980," n.d., available at [http://www.nfl.com/history/chronology/1971-1980].

⁷⁷ The Business of Football 2001, p. 394.

⁷⁸ National Football League, "History, 1971-1980."

⁷⁹ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 4.

⁸⁰ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players."

- 1982. The strike-shortened season resumed after the CBA was ratified on November 21-22. The CBA included, among other things, increases in players' medical, insurance, and retirement benefits; and a severance pay system.⁸¹ Players also gained rights related to their medical care: the right to a second opinion, the "right to select a surgeon for injury-related operations, and the right to inspect their club medical records."⁸²
- 1987. The 1982 CBA expired. The 1987 season included a strike, the use of replacement players, the NFLPA filing an antitrust lawsuit against the NFL and then filing charges with the National Labor Relations Board (NLRB), alleging unfair labor practices. A "special payment program was adopted to benefit nearly 1,000 former NFL players who participated in the League before the current Bert Bell NFL Pension Plan was created and made retroactive to the 1959 season. Players covered by the new program spent at least five years in the League and played all of part of their career prior to 1959. Each vested player would receive \$60 per month for each year of service in the League for life." Players continued to play through the 1993 season without a new CBA.
- 1987 and 1988. The owners agreed to allow benefit credits to accrue at the then-rate of \$150 per Credited Season.⁸⁵
- 1989. A court ruling in the NFLPA's antitrust lawsuit suggested that "players had to choose between being a union and using their right to strike under labor laws, or relinquishing their union rights and [pursuing] their antitrust rights as individuals in court." Players ratified a decision for the NFLPA to decertify as a union, which freed the players to pursue their antitrust rights. Team owners refused to allow continued accruals of benefit credits. Instead, owners created their own plan, called the "Pete Rozelle NFL Player Retirement Plan." The Rozelle plan was similar to the Bell plan, "except that it [Rozelle plan] was run totally by the owners and had

⁸¹ National Football League, "History, 1981-1990," n.d., available at [http://www.nfl.com/history/chronology/1981-1990]; Peter King, "The Surreal Strike of 1987," *Sports Illustrated*, Oct. 15, 2007, p. 22; NFL Players Association, "About Us: NFLPA History"; Stephen Fox, *Big Leagues, Professional Baseball, Football, and Basketball in National Memory* (Lincoln, NE: University of Nebraska Press, 1994), p. 426; Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 4.

⁸² NFL Players Association, "About Us: NFLPA History."

⁸³ Ibid.; The Business of Football 2001, p. 395.

⁸⁴ National Football League, "History, 1981-1990."

⁸⁵ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 4.

⁸⁶ NFL Players Association, "About Us: NFLPA History."

no player trustees."⁸⁷ By comparison, the union had the right to appoint three of the Bert Bell Plan's six voting trustees. The owners refused "to make further contributions [to the Bell Plan], and the trustees appointed by the union ... sued the trustees appointed by the owners."⁸⁸

- 1990. The NFLPA was re-formed as a professional association. Its goal was to "pursue litigation on behalf of individual players...." The change in status of the NFLPA "caused a rapid domino effect in court cases." For example, the NLRB awarded back pay to 1,400 players prevented from playing for one week after they ended their strike in 1987; a case filed in 1990 "resulted in a jury awarding damages to players; and the 1989 *Brown v. NFL* case awarded \$30 million to practice squad players...."
- 1992. "The NFL agreed to provide a minimum of \$2.5 million in financial support to the NFL Alumni Association and assistance to NFL Alumni-related programs. The agreement included contributions from NFL Charities to the Pre-59ers and Dire Need Programs for former players."
- 1993. The NFL and the players association signed a seven-year CBA, "which guarantee[d] more than \$1 billion in pension, health, and post-career benefits for current and retired players..." Specifically, the agreement provided for free agency; gave players a guaranteed percentage of the gross revenues; retroactively increased pre-59ers' pensions by 30% and all other players' pensions by 40%; added pre-59ers to the Bert Bell Pension Plan (which added 906 players to the plan); decreased the vesting requirement to three credited seasons; and established the Retiree Medical benefit, Second Career Savings Plan, and Total and Permanent (T&P) Disability benefits. Additionally, "WWII years were included for

⁸⁷ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 4.

⁸⁸ Ibid.

⁸⁹ NFL Players Association, "About Us: NFLPA History."

⁹⁰ The Business of Football 2001, p. 396.

⁹¹ National Football League, "History, 1991-2000," available at [http://www.nfl.com/history/chronology/1991-2000].

⁹² Ibid.

⁹³ NFL Players Association, "About Us: NFLPA History"; NFL Players Association, "Recent Pensions & Disability Improvements Timeline," n.d., available at [http://www.nflpa.org/pdfs/NewsAndEvents/Timeline_of_NFLPA_Pension_and_Disability_Improvements.pdf], downloaded Sept. 2007, on file with the author; NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 5; and Letter (continued...)

pension eligibility, increasing [the number of] credited seasons for 159 players," and "Korean War and Vietnam years were included for pension credits, adding 182 players." A single plan counsel (Groom Law Group) and a single plan actuary (Aon Corporation) were selected. The CBA "based future contributions strictly on negotiated actuarial factors." The Pete Rozelle Plan and its assets merged with the Bert Bell Plan, and the NFLPA becomes a certified union again. 96

- 1998. The 1993 CBA was extended through at least 2003. The extension established an annuity plan; provided for salary guarantees for certain players; increased minimum salaries, increased the lowest benefit credit from \$80 to \$100; increased the T&P disability benefit; and changed the pension eligibility requirement from five to four credited seasons.⁹⁷
- 2002. The CBA was extended again. The extension allowed injured reserve seasons prior to 1970 to be counted toward pension eligibility and raised the lowest benefit credits from \$100 to \$200.98
- 2006. The CB0A was extended and became effective until the last day of the 2012 league year. The extension raised the lowest benefit credit from \$200 to \$250 (for individuals who played during the period1920-1982); tripled widows' and surviving children's benefits; created the Plan 88 program; and increased the monthly pension amount by 10% for individuals who played from 1983-2006.⁹⁹
- 2007. The following benefits and programs were announced or established: Health Reimbursement Account Plan, Cardiovascular

^{93 (...}continued) from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, pp. 4-5.

⁹⁴ NFL Players Association, "Recent Pensions & Disability Improvements Timeline."

⁹⁵ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 5.

⁹⁶ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p.5.

⁹⁷ NFL Players Association, "About Us: NFLPA History"; NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 6; Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 5; and NFL Players Association, "Recent Pensions & Disability Improvements Timeline."

⁹⁸ Ibid.; NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 6.

⁹⁹ NFL Players Association, "Recent Pensions & Disability Improvements Timeline"; NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 6.

Health Program, NFL Player Joint Replacement Benefit Plan, and assisted living arrangements. ¹⁰⁰

• 2008. The following changes and programs were announced or established: expanded health screening that focuses on cardiovascular health, obesity, and prostate cancer; discounted rates and special services at three national assisted living providers; and a prescription drug card that will allow former players to purchase prescription medications at a discount. Additionally, the NFL and NFLPA announced changes that have been, or will be, made to T&P and LOD disability benefits. These changes are noted in Table 4.

How Benefits Are Funded

Funds for benefits that are included in the CBA come from the portion of the league's total revenues that is allocated to the players. A summary of the definition of "total revenues" (TR) is as follows:

[T]he aggregate revenues received or to be received on an accrual basis ... by the NFL and all NFL Teams ... from all sources, whether known or unknown, derived from, relating to or arising out of the performance of players in NFL football games, with only the specific exceptions set forth below [in Article XXIV, Section 1(a)(ii) of the CBA].... Total Revenues shall include, without limitation: ... gate receipts ... the sale, license or other conveyance of the right to broadcast or exhibit NFL preseason, regular season and playoff games on radio and television ... revenues derived from concessions, parking, local advertising, signage, magazine advertising, local sponsorship agreements, stadium clubs, luxury box income ... Internet operations... and sales of programs and novelties..." 102

Under the current CBA, the portion of total revenues that goes to players (that is, the "player costs percentage" each year is as follows:

Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 5; National Football League, "NFL & NFL Players Association Create New Joint Replacement Benefit Plan," news release, Dec. 10, 2007; and "14 Leading Medical Institutions Selected to Assist Retired Players Needing Joint Replacement Surgery," news release, Dec. 10, 2007. Few details are available about some of these initiatives, which means that eligibility criteria, the application process (if any), and the extent of benefits are unknown.

National Football League and NFL Players Association, "NFL and NFL Players Association Expand Disability Benefits Program for Retired Players," Feb. 29, 2008, available at [http://www.nflplayers.com/user/content.aspx?fmid=178&lmid=443&pid=422&type=n], p. 3. Detailed information about these initiatives is provided later in this report.

¹⁰² National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, pp. 82-83.

Player costs include "the total Salaries and Benefits attributable to a League Year for all NFL Teams under all of the rules set forth in Article XXIV (Guaranteed League-wide Salary, Salary Cap & Minimum Team Salary), but not including loans, loan guarantees, (continued...)

2006: 57%
2007: 57%
2008: 57.5%
2009: 57.5%
2010: 58%
2011: 58% 104

The amount of money equivalent to the player costs percentage in a given year is allocated between active players' salaries and benefits for both active players and retired players. The following description of how a team's salary cap is determined shows the relationship between salaries and benefits: in 2008, the amount of a team's salary cap will be "57.5% of Projected Total Revenues, less League-wide projected benefits, divided by the number of Teams playing in the NFL during such year...." The following definition of "benefits" lists the different benefits for active players and former players that are funded in the manner described above:

Benefits "mean the aggregate for a League Year of all sums paid ... by the NFL and all NFL Teams for, to, or on behalf of present or former NFL players, but only for: (i) pensions funding, including the Bert Bell/Pete Rozelle NFL Player Retirement Plan ... and the Second Career Savings Plan ...; (ii) Group insurance programs, including life, medical, and dental coverage ... and the Second Career Savings Plan; (iii) Injury protection ...; (iv) Workers' compensation, payroll, unemployment compensation, social security taxes, and contributions to the fund described in Article LIV, Section 4 below [Worker's Compensation Offset Provisions]; (v) Pre-season per diem amounts ... and regular season meal allowances ...; (vi) Expenses for travel, board and lodging for a player participating in an off-season workout program ...; (vii) Payments or reimbursements made to players participating in a Club's Rookie Orientation Program ...; (viii) Moving and travel expenses ...; (ix) Postseason pay ...; and salary paid to practice squad players ...; (x) Player medical costs ...; (xi) Severance pay ...; (xii) The Player Annuity Program ...; (xiii) The Minimum Salary Benefit ...; (xiv) The Performance Based Pool ...; (xv) The Tuition Assistance Plan ...; (xvi) The NFL Players Health Reimbursement Account ...; (xvii) The "88 Benefit" ...; (xviii) The NFL Player Benefits Committee..." 106

The portion of the "League-wide projected benefits" needed "to fund the Retirement Plan is calculated actuarially, in accordance with federal law." The

^{103 (...}continued)

unpaid grievances attributions, and unearned incentives." (National Football League and NFL Players Association, *NFL Collective Bargaining Agreement, 2006-2012*, p. 7.)

NFL Players Association, "NFLPA Term Sheet - Basic Economic Terms," Mar. 7, 2006, available at [http://www.nflpa.org/pdfs/CBA/2006_CBA_Extension_Term_Sheet.pdf], downloaded Sept. 2007, on file with the author.

¹⁰⁵ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 96.

¹⁰⁶ Ibid., pp. 93-94.

¹⁰⁷ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 29.

same is also true for the Health Reimbursement Account Plan. (The retirement plan and the Health Reimbursement Account Plan are described below.) According to the NFL and the NFLPA, the actuarial assumptions, or factors, that are used are negotiated during the collective bargaining process and are "acceptable to the plan's Enrolled Actuary." The following excerpt from the CBA describes the process:

For the 1993 Plan Year and continuing for each Plan Year¹¹⁰ thereafter that begins prior to the expiration of the Final League Year,¹¹¹ a contribution will be made to the Retirement Plan on behalf of each NFL Club as actuarially determined to be necessary to fund the benefits provided in this Article [of the CBA], based on the actuarial assumptions and methods contained in Appendix J [of the CBA]. No provision of this Agreement will eliminate or reduce the obligation to provide the benefits described in this Article, or eliminate or reduce the obligations of the NFL Clubs to fund retirement benefits. Contributions will be used exclusively to provide retirement benefits and to pay expenses.¹¹²

Similar language is found in the Bert Bell/Pete Rozelle NFL Player Retirement Plan:

For each Plan Year that begins prior to the expiration of the Final League Year, a contribution to the Trust [the trust agreement for the Retirement Plan] will be made by the Employers, as actuarially determined to be necessary to fund the benefits provided in this Plan based on the actuarial assumptions and methods contained in Appendix A [of the Retirement Plan].¹¹³

Funding for benefits other than the retirement plan and the Health Reimbursement Account apparently is not calculated using actuarial methods and assumptions. The NFLPA has stated that "[t]he contribution necessary to fund other benefit plans is more simply calculated as the total of the benefits provided plus all costs of administration. For the new 88 Plan, the consultants estimated an initial

¹⁰⁸ Ibid.

Letter from Goodell to Reps. Conyers and Smith, p. 10; NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 5. In 1993, a single plan counsel, Groom Law Group, and a single plan actuary, Aon Corporation, were selected for the retirement plan. (NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 5.)

¹¹⁰ "'Plan Year' means a 12-month period from April 1 to March 31. A Plan Year is identified by the calendar year in which it begins." (*Bert Bell/Pete Rozelle NFL Player Retirement Plan*, Apr. 1, 2001, p. 6.)

¹¹¹ Final League Year is "the League Year which is scheduled prior to its commencement to be the final League Year of the Collective Bargaining Agreement." A "League Year" is "the period from February 20 of one year through and including February 19 of the following year, or such other one year period to which the NFLPA and the [NFL's] Management Council may agree." (*Bert Bell/Pete Rozelle NFL Player Retirement Plan*, pp. 4 and 6.)

¹¹² National Football League and NFL Players Association, NFL Collective Bargaining Agreement: 2006-2012, p. 203.

¹¹³ Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 10.

contribution of \$1.88 million, all to benefit retired players."¹¹⁴ The method or methods used to determine how much money to allocate to this and other benefits is unknown.

Data provided by the NFL and the NFLPA show that possibly \$919.6 million was spent on benefits for retired players in 2006 and 2007. However, the ways in which the data are presented by the two organizations leave room for interpretation. The NFLPA states that "active players gave up approximately" the following amounts (which total \$181.6 million) during the period April 2006 through March 2007 for benefits for former players: 115

- \$96.5 million for retirement benefits for retired players;
- \$31 million for medical benefits for retired players (\$18 million for health reimbursement accounts, \$2 million for the 88 Plan, and \$11 million for "five years post-retirement fully paid health care");
- \$20 million for disability benefits for retired players; and
- \$34.1 million to fund workers' compensation coverage. 116

In fall 2007, the NFLPA also noted that 38% of vested former players were receiving monthly benefits at that time. 117

According to the NFL, "... clubs contributed approximately \$388 million" in 2006 to fund the Supplemental Disability Plan, Second Career Savings Plan, Annuity Program, Group Insurance Plan, Health Reimbursement Account Plan, 88 Plan, Severance Plan, and Tuition Reimbursement (which is not included in this report). The NFL estimated that the costs of these benefits in 2007 would be \$350 million.

Although the NFLPA regularly describes the amount of funds provided for retirees' benefits in terms of how the "[b]enefit costs reduce the revenue available for active players under the" CBA, it appears that this description refers to the process described above for the allocation of funds for benefits. Regarding the NFL's statement that the teams contribute funds for benefits, it seems plausible that this statement, too, refers to the allocation process described above.

The differences in the information provided by the NFL and NFLPA make it difficult to determine exactly how much money was spent for each benefit in 2006

¹¹⁴ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 29.

the "[b]enefit costs reduce the revenue available for active players under the" CBA. (NFL Players Association, "NFLPA White Paper" n.d., available at [http://www.nflpa.org/whitepaper/], downloaded Sept. 2007, on file with the author, p. 4.) This description appears to refer to the allocation process described above in this report.

Letter from Upshaw to Reps. Convers, Smith, Sanchez, and Cannon, pp. 29-30.

¹¹⁷ Ibid., p. 9.

The NFL will have contributed a total of \$2.2 billion for these benefits during the period 1998-2007. (Letter from Goodell to Reps. Conyers and Smith, p. 12.)

¹¹⁹ NFL Players Association, "NFLPA White Paper," p. 4.

or 2007. The NFLPA provided information that covers both years, while the NFL provided an amount for each year. Additionally, the NFLPA provided a breakdown by type of benefit (that is, retirement benefits, medical benefits, and disability funds) and amount, while the NFL provided an aggregate amount for eight different benefits, each of which is listed by the name of the benefit.

Benefits for Former Players

Table 4 provides a summary of the benefits available to former players; eligibility requirements vary by benefit. This overview includes selected features for each type of benefit. For detailed information about a particular benefit, it is best to consult the appropriate document, such as the CBA. Workers' compensation is included because, although states administer workers' compensation programs, the NFLPA and the NFL provide funding for workers' compensation for their players.

The following is a list of the benefits included in **Table 4**. Shortened names are used in the table because this format makes it easier to identify the description or purpose of the benefit. Each benefit is identified by its complete name, as well as a shortened version. For example, the NFL Players Health Reimbursement Account appears as "Health Reimbursement Account" in the table. An asterisk identifies a benefit that is included in the CBA.

- 88 Benefit (or Plan)*
- Cardiovascular Health (CVH) Program
- Bert Bell/Pete Rozelle NFL Player Retirement Plan Death Benefits ("death benefits")*
- Bert Bell/Pete Rozelle NFL Player Retirement Plan Line-of-Duty Disability ("line-of-duty disability")*
- Bert Bell/Pete Rozelle NFL Player Retirement Plan Retirement Benefits ("retirement benefits" or "pension")*
- Bert Bell/Pete Rozelle NFL Player Retirement Plan Total and Permanent Disability Benefits ("total and permanent disability benefits")*
- NFL Player Annuity Program ("annuity program")*
- NFL Player Joint Replacement Benefit Plan ("joint replacement benefit plan")
- NFL Player Second Career Savings Plan ("second career savings plan")*
- NFL Player Supplemental Disability Plan ("supplemental disability plan" or "supplemental disability benefits")*

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- NFL Players Health Reimbursement Account ("health reimbursement account")*
- Retiree Medical* (This benefit is part of Group Insurance, which is how the benefit is listed in the CBA. The remainder of the Group Insurance benefit is available to only active players.)
- Severance Pay*
- Workers' Compensation

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Table 4. Selected NFL-NFLPA Benefits as of October 2007

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
88 Plan ^{d,e} February 1, 2007	All years	Vested player who is suffering from dementia.	— Plan will reimburse, or pay for, certain costs related to dementia. — A maximum of \$88,000 may be paid annually for expenses for care provided by a third party (for example, institutional custodial care or home custodial care provided by an unrelated third party). The maximum amount of this benefit is \$50,000 annually for care that is not provided by a third party (for example, a relative provides care at home).
Annuity Program ^d April 1, 1998	1998-present	Minimum of four credited seasons.	 This is a deferred compensation program. An allocation of \$65,000 will be made for each eligible player who earns a credited season in an annuity year and who has a total of four or more credited seasons as of the end of such annuity year.
Cardiovascular Health (CVH) Program July 25, 2007	All years	Apparently, this program is open to all players.	— Provides cardiovascular screening and education.
Death Benefits ^d September 19, 1962	All years	Vested inactive or active player.	 — Provides financial assistance to widow and/or surviving minor children of a former or active player. — Monthly benefit equal to \$3,600 or 50% of the player's benefits, whichever is greater. For first 48 months after player's death, the amount of the benefit cannot be less than \$6,000/month for a player who was an active player after 1976 plan year, or \$9,000/month for a

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
			player who was an active player after the 1981 plan year. — For a widow, benefit ends with her death or remarriage. For children, benefit ends upon reaching the age of 19 (or 23, if in college). Termination based on age does not apply if child is mentally or physically incapacitated.
Health Reimbursement Account (HRA) ^d March 1, 2007	2004-present	At least eight credited seasons for a player whose last credited season was 2004 or 2005. At least three credited seasons for a player who earned a credited season in 2006 or any later year.	— An annual contribution is made to a player's account in the amount of \$25,000 or \$50,000, depending upon the terms of the CBA. Total contributions shall not exceed \$300,000. — Player may receive reimbursement for medical care expenses only during periods of time when he is not covered by the Group Insurance in the CBA or the Extended Post-Career Medical and Dental Insurance in the CBA.
Joint Replacement Benefit Plan 2007 ^f	All years	Unknown.	 — Assists retired players who need joint replacement surgery. — Plan provides financial assistance to all eligible former players to cover the cost of surgery. — Additional financial assistance is available from the NFL Player Care Foundation.
Line of duty (LOD) disability benefit ^d April 1, 1970	All years	Any player who incurs a substantial disablement (but is not totally and permanently disabled) arising out of NFL football activities, as	 — Amount of monthly benefit will equal the sum of the player's benefit credits (see Retirement Benefits) or \$1,000, whichever is greater. — Payments continue for duration of substantial disablement, but no longer than 7 ½ years.

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
		determined by the Retirement Board or the Disability Initial Claims Committee (DICC), that is a significant factor in causing his retirement from football. Player does not have to be vested.	 If both an LOD benefit and a T&P benefit are payable, only the larger of the two benefits will be paid. Application for LOD benefit must be submitted within 48 months after player ceases to be an active player.^g
Retiree Medical ^{d,h} May 6, 1993	1993-present	Vested.	 Active players receive group insurance benefits: life insurance, and medical and dental benefits. The same medical and dental benefits are provided to former players for a set amount of time, as described below. Players released or who otherwise severed employment after the first regular season game in the 2002 season, but before the first regular season game in 2005 season, continue to receive medical and dental benefits for 48 months. Players released after the first regular season game in the 2005 season and prior to the expiration or termination of the 2006-2012 CBA will receive medical and dental benefits for the following 60-month period.
Retirement Benefits ^{d,i} September 19, 1962	All years	Vested player.	— A player earns a benefit credit for each credited season, and a vested player's monthly pension is the sum of his benefit credits for each of his credited seasons. Under the 2006-2012 CBA, the benefit credits are as follow:

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
_	•	Criteria	Credited Season
			annuity. If a player receives an early payment benefit, his monthly pension will be based upon 75% of the sum of his benefit credits. — A player who chooses an early payment benefit after March 31,

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
			1982, will have any subsequent payments for certain benefits (for example, total and permanent disability benefits, line-of-duty disability benefits) reduced by 25%.
Second Career Savings Plan ^d July 1, 1993	1993-present	A first-year player may contribute to the plan. A player must have at least two credited seasons, at least one of which is for Plan Year 2006 or later, in order to receive a club contribution.	— Matching contributions shall be two dollars for each dollar provided by a player. The maximum matching contributions, which vary by plan year under the CBA, are as follow: \$20,000 for each year, 2006-2008; \$22,000 for 2009; \$24,000 for 2010, and \$26,000 for 2011. — Beginning at age 45, a player may withdraw money from his account.
Severance Pay ^d November 16, 1982	1982-present	Minimum of two credited seasons. At least one of the seasons must have occurred during the period 1993-2011. Player's written request for severance pay must indicate that he intends to permanently sever employment as an active player.	— A player's severance pay will equal the sum of the following: \$5,000 per credited season for each season during the period1989-1992; \$10,000 per credited season for each season during the period 1993-1999; \$12,500 per credited season for each season during the period 2000-2008; and \$15,000 per credited season for each season during the period 2009-2011. — Severance pay is paid in a single lump sum. Payment date varies depending upon when the individual was last involved in a league playing activity and when he submits an application.
Supplemental Disability Plan ^{d,1} July 1, 1993	1993-present	Former players who receive T&P disability benefits in the "active football," "active	 — Supplemental disability plan benefits are automatically paid to each eligible player. — Effective April 1, 2000, the monthly and annual supplemental

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
		nonfootball," and "football degenerative" categories.	disability plan benefit for each category is as follows: "active football," \$14,670 monthly and \$176,040 annually; "active nonfootball," \$7,167 monthly and \$86,004 annually; and "football degenerative," \$5,167 monthly and \$62,004 annually." — Players who receive T&P "inactive" category benefits do not receive any benefits under this plan."
Total and Permanent Disability Benefit ^{d,h,n} April 1, 1970	All years, except for an inactive player who does not have a credited season after 1958.	Active player (he does not have to be vested) or vested inactive player who is totally and permanently disabled, as determined by the Retirement Board or the DICC.	— The amount of a player's benefit will be equal to the sum of his benefit credits, excluding benefit credits for credited seasons prior to 1958. The benefit amount may be increased as follows for each benefit category: (a) Active football: monthly benefit will be not be less than \$4,000 if the disability or disabilities arise out of NFL football activities, arise while the player is an active player, and cause the player to be totally and permanently disabled "shortly after" the disability or disabilities first arise. (b) Active nonfootball: monthly benefit will not be less than \$4,000 if the disability or disabilities do not result from NFL football activities, but do arise while the player is an active player, and cause the player to be totally and permanently disabled "shortly after" the disabilities first arise. (c) Football degenerative: monthly benefit will not be less than \$4,000 if the disability or disabilities arise out of NFL football activities and result in T&P disability before 15 years after the end of the player's last credited season.

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
			(d) Inactive: The monthly benefit will not be less than \$1,500 (\$1,750 for applications received on or after April 1, 2007) ^p if the T&P disability or disabilities arise from other than NFL football activities while the player is a vested inactive player, or the disability or disabilities arise out of NFL football activities and result in total and permanent disability 15 or more years after the end of the player's last credited season, whichever is later. (e) Dependent child: monthly benefit will increase \$100 per each child who is a dependent. ^q — Effective for payments made on and after November 1, 1998, a player may receive a T&P payment for a disability resulting from a psychological/psychiatric disorder. This provision applies only to the "active nonfootball" and "inactive" categories, and special rules that pertain to disabilities resulting from other than a football injury. — A T&P disability that is a result of a psychological/psychiatric disorder may be awarded under the provisions for "active football" and "football degenerative" disabilities (and under special rules that pertain to disabilities resulting from a football injury incurred while an active player) if the requirements for such a disability are met and the disorder "(1) is caused by or relates to a head injury (or injuries) sustained by a Player arising out of League football activities (e.g., repetitive concussions); (2) is caused by or relates to the use of a substance prescribed by a licensed physician for an injury (or injuries) or illness sustained by a Player arising out of League football activities; or (3) is

Name of Benefit or Program and Year Established	Players from These Years May Participate	Summary of Eligibility Criteria ^a	Selected Features ^{b,c}
			caused by an injury (or injuries) or illness that qualified the Player for total and permanent disability benefits under Section 5.1(a) [active football]." — T&P benefit is payable for life or until cessation of total and permanent disability.
Workers' Compensations	All years	Apparently, all players are eligible. However, workers' compensation is regulated and administered by state governments, which also means that eligibility requirements and other details vary from state to state.	 — NFLPA has made arrangements for all players to be covered by workers' compensation, which is available to employees who have been injured or disabled on the job. — Workers' compensation may include disability pay or wage loss benefits, a lump sum benefit to compensate for permanent loss of function, and/or payment or reimbursement for medical expenses.

Sources: National Football League and NFL Players Association, NFL Collective Bargaining Agreement: 2006-2012, Mar. 8, 2006; NFL Players Association, "Line of Duty Disability," Mar. 12, 2008, available at [http://www.nflplayers.com/user/content.aspx?fmid=178&lmid=443&pid=367&type=n]; NFL Players Association, "NFLPA and NFL Announced New Retirement Benefit Initiatives," news release, July 25, 2007; Bert Bell/Pete Rozelle NFL Player Retirement Plan, Apr. 1, 2001; NFL Player Supplemental Disability Plan, Apr. 1, 2001; Letter from Eugene Upshaw, Executive Director, NFL Players Association, to Reps. John Conyers, Jr., Lamar S. Smith, Linda T. Sanchez, and Christopher B. Cannon, Nov. 5, 2007, p. 1; NFL Players Association, "CBA: Workers' Compensation Benefits," available at [http://www.nflpa.org/CBA/Workers_Comp.aspx] as of Nov. 15, 2007, on file with the author; National Football League, "NFL & NFL Players Association Create New Joint Replacement Benefit Plan"; and National Football League "14 Leading Medical Institutions Selected to Assist Retired Players Needing Joint Replacement Surgery," news release, Dec. 10, 2007; and Gregory P. Guyton, "A Brief History of Workers' Compensation," Iowa Orthopaedic Journal, 1999, available at [http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1888620].

Note: See the glossary in Appendix A for the definition of terms, such as "credited season," "plan year," and "vested player."

- a. Since this is only a summary, additional criteria or conditions may apply.
- b. The actual amount that a particular individual receives is determined by a number of factors, including, for example, the years in which he played and whether the amount of a particular benefit is altered by a succeeding CBA. Also, the receipt of a certain benefit may affect the amount of another benefit an individual receives. For example, receipt of an 88 Plan benefit may result in a decrease in Total and Permanent disability benefits as follows: "The maximum benefit payable for any month shall be reduced, but not below zero, by the amount of any total and permanent disability benefits paid by the Bert Bell/Pete Rozelle NFL Player Retirement Plan and the NFL Player Supplemental Disability Plan. However, the maximum benefit payable for any month shall not be reduced by those total and permanent disability benefits paid to players who are receiving the Inactive total and permanent disability benefit described in Section 5.1(d) of the Bert Bell/Pete Rozelle NFL Player Retirement Plan." (National Football League and NFL Players Association, NFL Collective Bargaining Agreement: 2006-2012, Mar. 8, 2006, pp. 215-216.)
- c. The amount, eligibility criteria, and other details of a particular Retirement Plan benefit may change over the years as new CBAs are negotiated and the Retirement Plan is changed accordingly. The details of other (non-retirement plan) benefits may be changed, too, by the NFL and the NFL Players Association.
- d. This benefit plan or program is included in the CBA.
- e. The 88 Plan was so named to honor John Mackey, a former Baltimore Colts tight end and member of the Hall of Fame who wore number 88. (NFL Players Association, "NFLPA White Paper," n.d., available at [http://www.nflpa.org/whitepaper/], p.23.), downloaded Sept. 2007, on file with the author.
- f. The NFL announced in Dec. 2007 the establishment of the Joint Replacement Benefit Plan, but it appears that implementation will occur at some later date.
- g. As announced on Feb. 29, 2008, the NFL and the NFLPA modified the deadline for applying for LOD benefits. A player will have 48 months or the number of credited seasons he has earned within which to apply. For example, a player who has six credited seasons will have six years, instead of four years, within which he must apply. The deadline will equal the number of credited seasons a player has, which means, for example, that a player with six credited seasons will have six years
- h. Retiree Medical is part of the Group Insurance benefit in the CBA, where it is identified as "Extended Post-Career Medical and Dental Benefits." It is unclear whether Retiree Medical covers injuries sustained as a player. The remainder of the Group Insurance benefit is available to only active players. (National Football League and NFL Players Association, NFL Collective Bargaining Agreement, 2006-2012, pp. 218-219.)
- i. A former player who is receiving T&P disability benefits when he reaches the normal retirement age of 55 will have his disability benefits converted to a retirement benefit (pension). The amount of the benefit will not change. (*Bert Bell/Pete Rozelle NFL Player Retirement Plan, Summary Plan Description*, Apr. 2005, p. 18.)
- j. For example, "[a]n Active Player for three or more games of the 1996 through 1999 seasons [would receive] Benefits Credits [in the amount of] \$1,465 (\$285 + \$330 + \$425 +\$425 = \$1,465). The player will, therefore, receive \$1,465 per month when he begins to receive his pension benefit at age 55." (NFL Players Association, "Rules and Regulations: Player Benefits," n.d., available at [http://www.nflpa.org/RulesAndRegs/PlayerBenefits.aspx] as of Aug. 21, 2007, on file with the author.)
- k. Specifically, the benefit credit of \$425 is for each credited season from 1998 "through the Plan Year that begins prior to the expiration of the Final League Year." (Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 11.)
- 1. Per the NFLPA, the Supplemental Disability Plan was created because, pursuant to federal statute(s), there is a cap on the amount of disability benefits a plan may pay, such as the retirement plan for former players. (Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 19.)
- m. See "Total and Permanent Disability Benefit" in the table for information about the four categories of T&P benefits.

- n. In Feb. 2008, the NFL and the NFLPA announced the following changes to the T&P disability benefit: "Players who took their NFL pension early, and are therefore ineligible to apply for and receive disability benefits, will be offered a new one-time opportunity to apply for total and permanent disability benefits. These players may establish their disability through either a medical examination or by a total and permanent disability determination from Social Security. The opportunity to apply for benefits will begin on April 1, 2008. Applications will be accepted through July 31, 2008. Players who have received a total and permanent disability determination from Social Security will not need to separately establish disability under the NFL plan. Players who were denied benefits under the NFL plan but have subsequently been found [to be] disabled by [the] Social Security [Administration] may have their NFL cases reconsidered. The other good news for retired NFL players is that NFL disability awards are not offset by the amount of any award paid by Social Security." (National Football League and NFL Players Association, "NFL and NFL Players Association Expand Disability Benefits Program for Retired Players," Feb. 29, 2008, available at [http://www.nflplayers.com/user/content.aspx?fmid=178&lmid=443&pid=422& type=n], p. 1.)
- o. "A Player who becomes totally and permanently disabled no later than six months after a disability(ies) first arises will be conclusively deemed to have become totally and permanently disabled 'shortly after' the disability(ies) first arises, as that phrase is used in subsections (a) and (b) above [descriptions of benefits for players who experience active football and active nonfootball disabilities], and Player who becomes totally and permanently disabled more than 12 months after a disability(ies) first arises will be conclusively deemed not to have become totally and permanently disabled 'shortly after' the disability(ies) first arises as that phrase is used in subsections (a) and (b) above. In cases falling within this six-to twelve-month period, the Retirement Board or the Disability Initial Claims Committee will have the right and duty to determine whether the 'shortly after' standard is satisfied." (Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 20.)
- p. The NFL and the NFLPA announced on Feb. 29, 2008, that "the minimum benefit post-career" for "non-football 'total and permanent' disability" had doubled from "\$20,000 to \$40,000 per year for retired players who become disabled unrelated to football." (National Football League and NFL Players Association, "NFL and NFL Players Association Expand Disability Benefits Program for Retired Players," p. 1.)
- q. A child is considered to be a dependent only until reaching the age of 19; if he or she is in college, age 23 is the threshold. (*Bert Bell/Pete Rozelle NFL Player Retirement Plan*, p. 4.)
- r. Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 21.
- s. The year that this benefit was established is unknown.

NFLPA Retired Players Department

The Retired Players Department, established in 1984,

acts to meet players' needs with the right services; continuously communicates and involves players of all ages to create an exclusive fraternity; works collaboratively with other NFLPA departments and Players Inc. 120 to give outstanding value to its members; provides leadership, administration, coordination and implementation to serve the needs of retired players and retired player chapters. 121

The department's objectives are

- "To establish more local chapters [of retired players]";
- "To increase the future pensions and benefits for all players";
- "To establish a formal line of communication between active and retired players";
- "To build a network of retired players for business contacts and second careers":
- "To help build the image of the game and promote it to the benefit of players; and"
- "To raise funds for the Players Assistance Trust (PAT)." 122

Accomplishments of the Retired Players Department include

• "[Assisting players] in gaining pension and disability benefit increases";

¹²⁰ "In September 2000, NFL PLAYERS and the NFL entered into a historic partnership to provide player group licensing rights to NFL sponsors. With this deal, NFL sponsors are given the right to utilize players as part of their sponsorship agreements.... Activities include marketing, licensing, special events, corporate sponsorship, media and content development, publishing, website (NFLPLAYERS.COM) and other promotional programs. PLAYERS INC is a fully integrated marketing company for active and retired NFL players. These activities generate guaranteed royalties to PLAYERS INC and the players, in addition to providing financial support to the NFLPA. The organization is committed to meeting the needs of all NFL players in the National Football League by creating player marketing opportunities, increasing brand awareness and developing valuable business partnerships." (NFL Players Association, "Sponsors/Licensees," available at [http://www.nflplayers.com/user/template.aspx?fmid=182&lmid=243&pid=0&type=1].) (Capitalization is in the original.)

 $^{^{121}\,}$ NFL Players Association, "Retired Players Department: FAQs," n.d., available at [http://www.nflpa.org/Faqs/Faqs.aspx?printer_friendly=yes] as of Nov. 2, 2007, on file with the author, p. 1.

¹²² Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 27.

- "[Administering] the PAT Fund, resulting in over \$5 million in payments on behalf of former players in need";
- "[Assisting] in networking between former players and potential employers";
- "Helping former players take advantage of workers compensation benefits under state law; and"
- "Providing the services of medical professionals in various areas including orthopedic and cardiovascular." ¹²³

Any player who had signed a contract with a team is eligible to join a chapter, and there are 33 chapters of former players across the country. ¹²⁴ Chapter presidents attend the annual chapter officers meeting and the Retired Players Convention. An election is held at the latter for the Retired Players Steering Committee, which is "the only elected national body representing retired players..."

Players Assistance Trust (PAT) Fund

The players association created the Professional Athletes Foundation (PAF), a 501(c)(3) organization under the Internal Revenue Code, in 1987. The foundation's mission is to "provide vocational, educational, recreational and athletic opportunities for people of all races, religions and nationalities, male and female, wherever they may live, including but not limited to needy, former, amateur and professional athletes and young people who might not have the fullest opportunity to develop their vocational and educational capabilities." ¹²⁷

In 1992, the foundation established the Player Assistance Trust (PAT) to "provide financial assistance to former professional and amateur players and their families..." Specifically, the PAT is to provide

short-term financial assistance to former players who find themselves in a financial crisis. A primary goal of the fund is to assist players who are faced with financial problems created by catastrophic illness.... The funds cannot be used for long-term financial support. Grants are not available for supplemental

¹²³ Ibid.

¹²⁴ Ibid., p. 26.

¹²⁵ NFL Players Association, "Retired Players Department: FAQs," p. 1.

¹²⁶ This organization is a tax-exempt organization under the Internal Revenue Code. For more information, see U.S. Dept. of the Treasury, Internal Revenue Service, "Exemption Requirements," available at [http://www.irs.gov/charities/charitable/article/0,,id=96099,00.html].

¹²⁷ NFL Players Association, "Retired Players Department: FAQs," pp. 4-5.

¹²⁸ Ibid., p. 5.

income to pension benefits. Grants are not available as loans for business transactions. 129

The maximum grant amounts available are \$10,000 for educational purposes and \$20,000 for financial or medical assistance; not every applicant, however, receives the maximum amount. 130

Donations from the players association, the NFL, and individuals, and a percentage of the fines levied against active players provide funding for the PAT. Since 2000 and through fall 2007, the amount of money from fines contributed to the PAT was \$2,814,692. The NFL has contributed the following amounts, which total \$6,350,000:

- 1997: \$350,000
- 1998: \$350,000
- 1999: \$350,000
- 2000: \$700,000
- 2001: \$700,000
- 2002: \$700,000
- 2003: \$700,000
- 2004: \$1,000,000
- 2005: \$1,250,000
- 2006: \$1,250,000¹³²

Data about grants awarded during the period 1991-2007 are provided in the following two tables. **Table 5** shows how many grants were awarded, by type (for example, education, financial, and medical). **Table 6** shows how many grants were awarded each year. A total of 860 grants have been awarded since the inception of the PAT, and, according to other information provided by the NFLPA, grants have been awarded to 662 different players and widows of players.¹³³

NFL Players Association, "Players Assistance Trust Fund Grant Guidelines," n.d., available at [http://www.nflpa.org/pdfs/Charitywork/PAT_Application_2007.pdf], downloaded Sept. 2007, on file with the author, p. 1.

¹³⁰ Ibid., p. 2.

¹³¹ Letter from Goodell to Reps. Convers and Smith, p. 12.

¹³² Ibid.

Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 28.

Table 5. Players Assistance Trust Fund Grants, by Grant Type, 1991-2007

Type of Grant	Number and Percentage of Grants ^a	Amount and Percentage of Money ^a
Education	92 11%	\$398,393.22 7%
Education/Financial	11 1%	\$72,597.66 1%
Financial	585 68%	\$3,861,965.46 70%
Medical	119 14%	\$698,313.49 13%
Medical/Financial	52 6%	\$473,941.67 9%
Unknown	1 <1%	\$3,315.00 <1%
Total	860	\$5,508,526.50

Source: Data provided by the NFL Players Association; calculations performed by the author.

Note: The data for 2007 may be incomplete as the data were provided before the end of 2007.

a. Percentages have been rounded.

Significant percentages of the number of PAT grants (88%) and the amount of money (92%) have been awarded for financial or medical purposes, or for a combination of the two. Only 12% of the grants, and 8% of the money, were awarded for education and education/financial purposes. The largest average grant, \$6,855.29, was for medical and medical/financial purposes. The average amount of a financial grant was \$6,601.65. The average amount of an education and education/financial grant was \$4,572.73. Overall, the average amount of a grant was \$6,405.26.

Table 6. Players Assistance Trust Fund Grants, by Year, 1991-2007

Year	Number and Percentage of Grants ^a	Amount and Percentage of Grants ^{a,b}	Average Amount of Grant ^b
1991	2 <1%	\$4,836 <1%	\$2,418
1992	19 2%	\$92,120 2%	\$4,848

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Year	Number and Percentage of Grants ^a	Amount and Percentage of Grants ^{a,b}	Average Amount of Grant ^b
1993	33 4%	\$134,937 2%	\$4,089
1994	25 3%	\$122,609 2%	\$4,904
1995	37 4%	\$190,019 3%	\$5,136
1996	48 6%	\$354,419 6%	\$7,384
1997	51 6%	\$341,975 6%	\$6,705
1998	46 5%	\$275,267 5%	\$5,984
1999	46 5%	\$387,044 7%	\$8,414
2000	17 2%	\$91,668 2%	\$5,392
2001	35 4%	\$210,493 4%	\$6,014
2002	32 4%	\$205,505 4%	\$6,422
2003	45 5%	\$281,239 5%	\$6,250
2004	56 7%	\$360,824 7%	\$6,443
2005	130 15%	\$867,392 16%	\$6,672
2006	143 17%	\$834,881 15%	\$5,839
2007°	95 11%	\$753,300 14%	\$7,929
Total	860	\$5,508,528	\$6,405

Source: Letter from Eugene Upshaw, Executive Director, NFL Players Association, to Reps. John Conyers, Jr., Lamar S. Smith, Linda T. Sanchez, and Christopher B. Cannon, Nov. 5, 2007, exhibit C; calculations performed by the author.

a. Percentages have been rounded.

b. Dollar amounts have been rounded to the nearest dollar.

c. The data for 2007 may be incomplete as the data were provided before the end of 2007.

Despite the possibility that the data for 2007 may be incomplete (for the reason stated above), over 40% of the grants were awarded during the years 2005-2007; 368 grants, 43% of the total, were awarded during this period. Accordingly, the percentage of grants awarded in each of these years is in double digits. For the previous 14 years, the percentage of grants awarded each year ranged from less than 1% to 7%. Consistent with these results, 45% (\$2,455,573) of the total amount of the grants was awarded during the period 2005-2007. The reasons for the relatively consistent percentage of grants for each year from 1991 through 2004, and the noticeable increase in 2005 followed by similarly high percentages in 2006 and 2007 are unknown. More former players needed assistance during these three years, but it is unclear whether the rise in the number of grants is related to, for example, the type and amount of benefits the players received from NFL/NFLPA-funded benefits and whether these benefits met their needs; wider dissemination of information about the PAT (if indeed information was disseminated more widely than had been done previously); or changes, if any, that were made to the PAT applications process.

Regarding the average amount of a grant, there has been a general upward trend. Aside from the initial year, when only two grants were awarded and the average grant amount was \$2,418, the average amount has increased from \$4,848 in 1992 to \$7,929 in 2007. However, the highest average amount, \$8,414, was in 1999, and the average amount in 2006 was \$5,839.

The NFL has noted that individual clubs also fund efforts involving former players; usually, these efforts are directed toward players who were members of a particular club.¹³⁴

The Alliance

In May 2007, four organizations — the NFL, the NFLPA, the NFL Alumni Association, and the Pro Football Hall of Fame — came together to form the "Alliance," which "is aimed at addressing the medical concerns and needs of retired players, including joint replacements, cardiovascular health programs and assisted living arrangements." In December 2007, the NFL announced the establishment of the NFL Player Care Foundation, which is "governed by representatives of members of the Alliance," and which apparently will administer the \$17 million that has been donated to date. In February 2008, the NFL and the NFLPA announced that four former players — Andre Collins, Willie Lanier, Randy Minniear, and Ozzie Newsome — had been appointed to the board of the directors for the NFL Player Care Foundation, and that these board members would select additional members.

¹³⁴ Letter from Goodell to Reps. Convers and Smith, p. 12.

 $^{^{135}}$ Ibid.; National Football League, "NFL Clubs Commit \$10 Million in Additional Funding to Retired Players for Medical Assistance."

¹³⁶ National Football League, "NFL & NFL Players Association Create New Joint Replacement Benefit Plan."

¹³⁷ National Football League and NFL Players Association, "NFL and NFL Players Association Expand Disability Benefits Program for Retired Players," p. 3.

The foundation will coordinate and provide funds to the programs established by the Alliance. 138

When the league and the players association announced, in July 2007, the formation of this group, they also announced that the Alliance had received \$7 million. ¹³⁹ NFL team owners approved a donation of an additional \$10 million in October 2007. ¹⁴⁰ Fines paid by active players to the NFL for on-field infractions, and contributions from the NFLPA, other members of the Alliance, and "other interested retired player groups" will supplement the \$17 million. ¹⁴¹

As part of this initiative, the NFL and the players association created the NFL Player Joint Replacement Plan in fall 2007. Fourteen medical centers have been selected to provide these services:

[The medical centers will] assist eligible retired players in need of joint replacement surgery.... The medical facilities, carefully chosen for their expertise, high-quality service and reputation, will make available specialized, coordinated care to players covered by this new program. The program provides a common application process to assist them gain access to the institutions. The plan also will provide financial assistance to all players, regardless of their financial situation, to cover the cost of the operations. For players not covered by insurance and who cannot pay for the procedure, additional financial assistance will be available from the newly created NFL Player Care Foundation. Players eligible for assistance from the NFL Player Care Foundation will not be responsible for the cost of either the joint replacement surgery or post-operative rehabilitation. ¹⁴²

As reported in *The New York Times*, only retired players who are vested are eligible for this benefit.¹⁴³

The following 14 institutions will provide joint replacement surgery: St. Vincent's Birmingham/Andrews Sports Medicine & Orthopaedic Center (Birmingham, AL), Broward General Medical Center (Ft. Lauderdale, FL), Centinela Freeman Regional Medical Center (Marina del Rey, CA), Cleveland Clinic Foundation (Cleveland, OH), Lenox Hill Hospital (New York, NY), MedStar Health — Georgetown University Hospital and Union Memorial Hospital (Washington,

 $^{^{138}}$ Information provided electronically by the NFL Players Association to the author on Mar. 3, 2008.

¹³⁹ NFL Players Association, "NFLPA and NFL Announce New Retirement Benefit Initiatives."

¹⁴⁰ National Football League, "NFL Approves Additional \$10 Million for Retired Players," news release, Oct. 24, 2007, available at [http://search.nfl.com/search/?query=recent&sort=date&page=5].

¹⁴¹ National Football League, "NFL Approves Additional \$10 Million for Retired Players."

¹⁴² National Football League, "NFL & NFL Players Association Create New Joint Replacement Benefit Plan," news release, Dec. 10, 2007.

¹⁴³ Frank Listky, "Rehab Plan Announced for N.F.L.'s Ex-Players," *New York Times*, Dec. 11, 2007, available at [http://www.nytimes.com/2007/12/11/sports/football/11joints.html].

DC, and Baltimore, MD, respectively), Methodist Hospital, (Houston, TX), Mount Sinai Medical Center (New York, NY), Northwestern Memorial Hospital (Chicago, IL), OASIS MSO, Inc. (San Diego, CA), St. Joseph's Hospital-Atlanta (Atlanta, GA), Texas Orthopedic Hospital (Houston, TX), and University of Pittsburgh Medical Center (Pittsburgh, PA). Houston, New York, the Washington, DC, metropolitan area, and the state of California have two facilities each that are on the list. The remaining six institutions are in Alabama, Florida, Georgia, Ohio, Illinois, and Pennsylvania. Without information about the location of former players, it is unknown how many retired players reside in or near these 10 cities or metropolitan areas.

Post-surgery rehabilitation and physical therapy will be provided to eligible former players by HCR Manor Care, which has 280 skilled nursing and rehabilitation centers and 85 outpatient rehabilitation therapy clinics across the country.¹⁴⁵

The Alliance has also developed the following programs:

Health screening — Two doctors, funded by the NFL Player Care Foundation, are working with medical centers throughout the country to make it easier for players to get cardiovascular screening without cost. Players found to need cardiovascular care will receive affordable medical, nutritional and other treatment. Obesity screening and education also is provided.

Prostate cancer screening — In conjunction with the American Urological Association, the Alliance will establish a comprehensive program of prostate cancer screening, care and education.

Assisted living arrangements — Negotiated discounted rates and special services are made available to former players at three leading national assisted living providers — Brookdale Senior Living, Inc.; Belmont Village L.P., and Silverado Senior Living, Inc.

Prescription drug card — The NFL and NFLPA are providing retired players with a prescription drug card that permits them to purchase prescription medications at a substantial discount. This new benefit is provided at no cost to former players. ¹⁴⁶

¹⁴⁴ Ibid.

¹⁴⁵ Ibid. Information about HCR Manor Care is available at [http://www.hcr-manorcare.com].

¹⁴⁶ National Football League and NFL Players Association, "NFL and NFL Players Association Expands Disability Benefits Program for Retired Players," p. 3. (Boldface included in original.)

Other Efforts to Aid Former Players

Selected Organizations and Websites

Several former players and other individuals have established organizations or websites with the goal of aiding retired players. Examples of these organizations and websites include the following:

- Dignity After Football Inc. This organization is "committed to giving a voice to past heroes of the NFL and to finally restoring dignity to the lives of thousands of disabled and under-pensioned former players." 147
- Fourth & Goal. Bruce Laird, a former NFL player, founded this organization to assist retired players. 148
- Gridiron Greats. "The Gridiron Greats Assistance Fund is a non-stock, non-profit corporation that has been established to provide financial assistance and coordination of social services to retired players who are in dire need due to a variety of reasons including inadequate disability and/or pensions."
- Hall of Fame Enshrinee Assistance Fund. One of the objectives of this organization "is to help its own by offering support to former pros experiencing financial or medical hardship."¹⁵⁰
- Hall of Fame Players Association. One of the association's six purposes is to "assist Hall [of Fame] members who have financial difficulties." Established in 2001, the Hall of Fame Players Association (HOFPA) Charitable Foundation "will contribute to local and national charities, create a relief fund for members who are in need and support awards and scholarship efforts in selected regional areas." 152

Dignity After Football Inc., "Mission," n.d., available at [http://www.dignityafterfootball.org/].

¹⁴⁸ Greg Johnson, "More NFL Players Donating Game Checks to Charity," *Los Angeles Times*, Dec. 12, 2007, available at [http://www.latimes.com/sports/football/nfl/la-sp-nfl12dec12,1,1897270. story?coll=la-headlines-sports-nfl].

Gridiron Greats, "About the Gridiron Greats Fund," available at [http://www.gridirongreats.org/aboutthefund.html].

¹⁵⁰ NFL Alumni, "Mission Statement," available at [http://www.nflalumni.org/].

¹⁵¹ Hall of Fame Players Association, "About Us," available at [http://www.hofplayers.com/index.asp?PageAction=Custom&ID=15].

¹⁵² Hall of Fame Players Association, "Charities," available at [http://www.hofplayers.com/index.asp?PageAction=Custom&ID=140].

- The John Mackey Fund, Inc. The fund was established "to raise public awareness and fund research to find a cure for Frontotemporal Dementias." ¹⁵³
- NFL Alumni Association's Dire Need Fund. This is a joint effort of the NFL and NFL alumni to provide "assistance to former NFL players and coaching staff members experiencing financial or medical hardship."¹⁵⁴
- Ralph Wenzel Trust. The trust was established initially to receive donations to help cover expenses for the care of Wenzel, who suffers from Alzheimer's-type dementia. Wenzel now participates in an NFL program ¹⁵⁵ that pays for a portion of his care, so the website continues as a tribute to Wenzel and as a means of collecting information about problems faced by former football players. ¹⁵⁶
- Retired Professional Football Players for Justice. This website was created "to inform former football players, fans and supporters of the actions being taken by retired players to collect what they fairly deserve, but that has not been distributed by the organizations that claim to be acting in the players' best interest."¹⁵⁷

Active Players' Efforts

In fall 2007, a lineman for the Kansas City Chiefs, Kyle Turley, announced that he would donate his paycheck from his team's game on December 23 to help retired players who are in need. Reportedly, Turley talked to approximately 20 players who said they will donate to Gridiron Greats, and he sent a letter to other players in late November on the subject of donations. Turley is quoted, in a *New York Times* article, as saying: "Are we going to wait until guys die? Are we going to wait until guys commit suicide before we make a difference and change this thing?" [He added:] "If this system doesn't get fixed, no matter how much money you make ... you are a serious surgery away from being broke." At least 12 other active players also have contributed funds to Gridiron Greats, and Turley's goal is to raise \$8

¹⁵³ The John Mackey Fund, Inc., available at [http://johnmackeyfund.org/].

NFL Alumni, "NFL Alumni Dire Need Charitable Trust," available at [http://www.nflalumni.org/dire_need.html].

¹⁵⁵ This statement may be a reference to the 88 Plan.

¹⁵⁶ Ralph Wenzel Trust, available at [http://www.ralphwenzeltrust.org].

Retired Professional Football Players for Justice, "About Us," available at [http://www.playersforjustice.org/aboutus.html].

^{158 &}quot;N.F.L. Players Plan to Donate to Retirees," *New York Times*, Nov. 27, 2007, available at [http://www.nytimes.com/aponline/sports/AP-FBN-NFL-Disability.html?ex= 1353906000&en=8264ea3f9c77d661&ei=5088&partner=rssnyt&emc=rss].

¹⁵⁹ Ibid.

million, according to another news article. Additionally, it has been reported that former tennis player John McEnroe, former NBA player Charles Barkley, and sports broadcaster Bob Costas have indicated that they will donate money to Gridiron Greats. 161

NFL and NFLPA Health and Safety Initiatives

As noted in the introduction to this report, a former player's disabilities (as interpreted broadly) or chronic health problems might, in some cases, have their origins in what occurred, or did not occur, while the individual was an active player in the NFL. A potentially significant factor for active players is the NFL's and the NFLPA's efforts to safeguard their health, safety, and general welfare. Such efforts may include, at a minimum: (1) keeping players informed of, and actively soliciting their suggestions and ideas on, health and safety issues and initiatives; (2) helping players prepare for the rigors of playing professional football; (3) identifying and mitigating all possible conditions and factors that could affect a player's health and safety; and (4) upon being made aware of a potentially unsafe or unhealthful condition, practice, piece of equipment, or rule or guideline, for example — which, in any case, could involve an act committed or omitted — acting in a timely fashion to remedy the situation. Some health or safety problems, such as excessive weight, concussions, and injuries to joints, might have significant, long-term implications for players. Thus, a comprehensive approach to the health and safety of players might also include research that examines the possible long-term effects or consequences of the different types of injuries sustained by players. 162

The material in this next section describes the league's and the players association's health and safety initiatives.

NFL Injury and Safety Panel

The NFL Injury and Safety Panel was founded in 1993. The panel

• "developed and manages an injury surveillance system that reports the types and severity of injuries that players experience each year. These reports are used by team medical staffs to assist in injury prevention and treatment, and by the Competition Committee to

¹⁶⁰ Pat Borzi, "Fund for N.F.L. Retirees in Need of Help Is Gaining Support," *New York Times*, Dec. 12, 2007, available at [http://www.nytimes.com/2007/12/12/sports/football/12veterans.html]; Greg Johnson, "More Players Donating Game Checks to Charity," *Los Angeles Times*, Dec. 12, 2007, available at [http://www.latimes.com/sports/football/nfl/la-sp-nfl12dec12,1,1897270.story?coll=la-headlines-sports-nfl&ctrack=1&cset=true].

¹⁶¹ Ibid.

¹⁶² As noted below, the NFL is planning to request or sponsor a study on the long-term effects of concussions.

assist in the development of playing rules that promote safety. Rules and enforcement are reviewed annually..."; and the panel¹⁶³

• "evaluates proposals and makes recommendations regarding grants to support research." ¹⁶⁴

The NFL has had the injury surveillance system since 1980, and team physicians and athletic trainers use it "to record data on injured players and circumstances surrounding injuries." The league produces two reports each year — one approximately midway through the regular season and the other after the Super Bowl — that are detailed medical analyses of the data submitted to, and maintained in, the injury surveillance system. The NFL provides a copy of each report to the NFLPA. 166

The panel's Subcommittee on Foot and Ankle Injuries, which was founded in 2005, "collects and analyzes injury data on foot and ankle injuries, works with shoe manufacturers to encourage the development of more protective equipment, and educates team equipment managers and medical staffs on these matters. The subcommittee has commissioned studies by Boise State University and Michigan State University analyzing how shoe and turf factors related to these injuries." ¹⁶⁷

The NFL does not know how many players decided to retire because of injuries they sustained while playing football. However, the league estimates that 181 players who retired during the period 1993-2004 may have done so because of such injuries.¹⁶⁸

NFL Cardiovascular Health Committee

The Cardiovascular Health Committee, which was established in 2004, consists of team physicians, athletic trainers, and experts in "cardiology and cardiovascular

¹⁶³ Letter from Goodell to Reps. Conyers and Smith, p. 8.

¹⁶⁴ Ibid.

¹⁶⁵ Elliot J. Pellman, et al., "Concussion in Professional Football: Epidemiological Features of Game Injuries and Review of the Literature," *Neurosurgery*, vol. 54, no. 1, Jan. 2004, p. 82.

¹⁶⁶ Personnel affiliated with the NFL have used data from the injury surveillance system for articles on NFL players and health issues. For example, see the preceding footnote. Additionally, data from the surveillance system were used in this article: Bryan T. Kelly, et al., "Shoulder Injuries to Quarterbacks in the National Football League," *American Journal of Sports Medicine*, vol. 32, no. 2, 2004, pp. 328-331.

¹⁶⁷ Ibid., p. 9.

¹⁶⁸ Ibid. The basis for the league's "assessment" is that 181 players received additional compensation that is available or provided to players who do not "pass their pre-season physical due to an injury sustained during the prior season and thus [are] unable to play." (Letter from Goodell to Reps. Conyers and Smith, p. 9.)

medicine, endocrinology and obesity, sleep medicine and cardiovascular disease epidemiology."¹⁶⁹ The committee's objectives are to investigate

the prevalence of cardiovascular risk factors in NFL players, including hypertension, diabetes, sleep apnea and obesity; [assess] how those risk factors relate to different body types and positions on the field; and [evaluate] the effect of cardiovascular risks on various aspects of an NFL player's life, such as aerobic training, nutrition, family history and demographics.¹⁷⁰

This committee also oversees the CVH program, which involves screening and education, for retired players.¹⁷¹

NFL Medical Research Grants

Through NFL Charities, a nonprofit organization that was established in 1973, the NFL awards charitable grants for sports-related medical research. Nonprofit educational and research institutions may apply for these grants, the focus of which must be "sports injury prevention, injury treatment, [or] other related research that affects the health and performance of athletes." Within the category of sports-related medical research grants, there are four subcategories: education, medical, MTBI, and scientific research. The following list shows what types of research or activities have been funded by each grant subcategory:

- Education grants are used to fund the National Athletic Trainers' Association Non-Medical Research and Scholarship Fund, the annual meeting of the NFL Physicians Society, and the Professional Football Athletic Trainers Society Foundation's Ethnic Minority Scholarship Program.
- Medical grants are used to pay the manager of the NFL's injury surveillance system and to pay for studies on concussions and cardiovascular disease.
- MTBI grants have paid for studies involving concussions and related subjects.

¹⁶⁹ Ibid., pp. 6-7. The former commissioner of the NFL selected the co-chairmen who, in turn, selected the other members of the committee. (Ibid., p. 7.)

¹⁷⁰ Ibid.

¹⁷¹ Ibid.

 $^{^{172}}$ National Football League, NFL Charities, "NFL Charities Grant Guidelines," available a t $\,$ [h t t p : / / w w w . n f l p a . o r g / p d f s / C h a r i t y W o r k / 2006NFLCHARITIESGRANTGUIDELINES.pdf], downloaded Sept. 2007, on file with the author.

¹⁷³ National Football League, "NFL Charities, Medical Research Grants," available at [http://www.jointheteam.com/programs/program.asp?p=39&c=6].

• Scientific research grants have funded studies on, for example, arthritis, heat illness, orthopedic injuries and treatments, and cardiac disease.¹⁷⁴

Table 7 shows the amount of money awarded for grants in each of the four subcategories.

Table 7. NFL Charities' Grants for Research Related to Players' Health, 2003-2007

	Total Amount of Grants by Subcategory								
Year	Education	Medical	МТВІ	Scientific Research					
2003	\$65,000	\$70,935	\$200,000	\$5,126,666					
2004	\$92,000	\$70,935	\$180,000	\$862,825					
2005	\$92,000	\$263,715	\$200,000	\$1,182,900					
2006	\$92,000	\$502,385	\$345,900	\$1,154,875					
2007	\$112,000	\$1,184,030	\$100,000	\$1,230,073					
Total	\$453,000	\$2,092,000	\$1,025,900	\$5,126,666					

Source: Letter from Roger Goodell, Commissioner, National Football League, to Reps. John Conyers, Jr., and Lamar S. Smith, Nov. 2, 2007, attachment 8.

The percentage of total funds awarded for grants, by subcategory and in descending order, is: scientific research, 59%; medical, 24%; mild traumatic brain injury, 12%; and education, 5%. Although the percentage of funds for MTBI grants might seem relatively small, some medical grants have been awarded for research into concussions, and the league's MTBI Committee has conducted numerous studies (see below and **Appendix B**).

NFL Mild Traumatic Brain Injury Committee

The Committee on Mild Traumatic Brain Injury was established in 1994, by then-Commissioner Paul Tagliabue. After addressing the definition of "concussion," undertaking an effort to collect data, and reviewing available safety equipment, the committee recommended to the commissioner that

the NFL should independently fund scientific research that would enable scientists to better understand the cause(s) of MTBI; that this research should be

¹⁷⁴ Letter from Goodell to Reps. Convers and Smith, attachment 8.

funded to independent scientific researchers; and that the NFL Mild Traumatic Brain Injury Committee should be charged with oversight of the project. ¹⁷⁵

To date, the committee has published 14 studies, all in the journal *Neurosurgery*, and has contributed to "the development of a clearer understanding of the nature of concussions in football, how they are caused, and the types of impacts that are more likely to result in concussions." The National Operating Committee on Standards for Athletic Equipment (NOCSAE), which, among other things, develops standards for and tests football helmets, and helmet manufacturers have received the committee's research. The National Operating Committee is the committee of the committee in the committee is research.

A list of members of the committee, and their professional affiliations, is found in **Appendix C**.

NFL and NFLPA Education Efforts for Players

Although the NFL has noted that "education regarding injuries and related matters is principally done by team medical staffs," the league has provided some information to players. In addition to the information on concussions disseminated by the league (see below), the NFL and the players association have prepared and distributed information on their substance of abuse policy and program, and their policy on anabolic steroids and related substances. Materials on heat and hydration that were developed by the NFL Physicians Society have been shared with team medical staffs. 180

For its part, the NFLPA has stated that it "does not conduct any formalized educational program for players concerning injuries, their treatment, or rehabilitation.

¹⁷⁵ Elliot J. Pellman, "Background on the National Football League's Research on Concussion in Professional Football," *Neurosurgery*, vol. 53, no. 4, Oct. 2003, pp. 797-798.

¹⁷⁶ Letter from Goodell to Reps. Convers and Smith, p. 5.

¹⁷⁷ Ibid., pp. 5-6. Additional information about the National Operating Committee on Standards for Athletic Equipment (NOCSAE) is available at [http://www.nocsae.org/].

¹⁷⁸ Letter from Goodell to Reps. Convers and Smith, p. 13.

The following substances are considered substances of abuse under the NFL-NFLPA policy: alcohol (under certain circumstances), cocaine, marijuana, amphetamine and its analogues, opiates, phencyclidine (PCP), and methylenedioxymethamphetamine (MDMA) and its analogues. (National Football League and NFL Players Association, *National Football League Policy and Program for Substances of Abuse*, 2007, available at [http://www.nflplayers.com/images/pdfs/RulesAndRegs/Drug_Policy_2007.pdf], pp. 6, 20.) The categories of prohibited substances included in the latter policy are anabolic agents (steroids), masking agents, and certain stimulants. (National Football League and NFL Players Association, *National Football League Policy on Anabolic Steroids and Related Substances* 2007, 2007, available at [http://www.nflplayers.com/images/pdfs/RulesAndRegs/BannedSubstances.pdf], pp. 13-16.) See CRS Report RL32894, *Anti-Doping Policies: The Olympics and Selected Professional Sports*, by L. Elaine Halchin, for additional information about the NFL's steroids policy and doping in general.

¹⁸⁰ Letter from Goodell to Reps. Convers and Smith, p. 13.

Under the standard NFL Player Contract form, Club medical staff has full discretion on the treatment of injuries, subject to the player's right to a second opinion and the right to choose his own surgeon should surgery become necessary." The players association provides free legal representation for grievances having to do with injuries; includes information on injury grievances and related topics in the Player Planner; maintains a list of physicians whom players may consult when seeking second opinions; and, though union representatives, brings issues related to injuries to the attention of the Joint Committee on Player Safety and Welfare. 182

NFLPA Medical Consultant and Performance Consultant

The NFLPA's medical consultant (or advisor) "participates in various studies conducted by the NFL and helps monitor compliance with a set of medical guidelines the NFL clubs have been advised to follow regarding acclimatization, emergency medical care, heat prostration, and other medical issues." It is unclear whether this individual is responsible for monitoring each team's compliance with the NFL's medical guidelines. In any case, the method used for monitoring, how often it occurs, and whether the medical consultant has a staff to aid him or her are unclear.

The extent of the medical consultant's responsibilities raises the following questions. Does the medical advisor personally monitor the teams, perhaps visiting each team on a regular basis; reviewing the team's policies, protocols, and other materials; reviewing a sample of players' medical records to see how players were treated; and talking with medical staff as well as players? Or do teams use a "self-report" model for compliance, whereby team staff members submit a verbal or written report to the medical advisor that indicates to what extent the team complies with medical guidelines?

The performance consultant attends NFLPA's annual meeting and "advises player reps [representatives] on a variety of health-related issues, including conditioning, rehabilitation of injuries, use of nutritional supplements, and proper equipment." ¹⁸⁴

¹⁸¹ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, pp. 30-31.

¹⁸² Ibid., p. 31. The Player Planner is an appointment book that the NFLPA provides to players and that includes information about, for example, benefits, the NFLPA, and the NFL season.

¹⁸³ Ibid., p. 11. Dr. Thom A. Mayer, CEO and president of BestPractices and chairman, Dept. of Emergency Medicine, Inova Fairfax Hospital, is the NFLPA's medical consultant. (Ibid.)

¹⁸⁴ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 11. The players association's performance consultant is Mark Verstegen, founder and chairman, Athletes' Performance, a personal training company.

NFL and NFLPA Joint Committee on Player Safety and Welfare

The following excerpt from the CBA describes the committee's composition, responsibilities, and authority:

A Joint Committee on Player Safety and Welfare (hereinafter the "Joint/ Committee") will be established for the purpose of discussing the player safety and welfare aspects of playing equipment, playing surfaces, stadium facilities, playing rules, player-coach relationships and any other relevant subjects. The Joint Committee will consist of six members: three Club representatives (plus advisors) and three NFLPA representatives (plus advisors). The Joint Committee will hold two regular meetings each year on dates and at sites selected by the Committee. Special meetings may be held at any time and place mutually agreeable to the Committee. The Joint Committee will not have the power to commit or bind either the NFLPA or the [NFL] Management Council on any issue. The Joint Committee may discuss and examine any subject related to player safety and welfare it desires, and any member of the Committee may present for discussion any such subject. Any Committee recommendation will be made only to the NFLPA, the Management Council, the Commissioner, or any appropriate committee of the NFL; such recommendation will be given serious and thorough consideration.¹⁸⁵

Pursuant to the 2006-2012 CBA, an additional task was assigned to the committee, which is as follows: "The NFLPA and the [NFL] Management Council agree that a task for the Joint Committee to undertake promptly upon the execution of this Agreement is a review of all current materials on the player safety aspects of player equipment, playing surfaces, including artificial turf and other safety matters." ¹⁸⁶

The NFLPA has the right to initiate an investigation "before the Joint Committee if the NFLPA believes that the medical care of a team is not adequately taking care of player safety." Two or more neutral physicians will investigate the issue raised by the NFLPA, write a report, and submit recommendations to the joint committee within 60 days of being selected. If the NFLPA disagrees with the outcome of this process, it is unclear what recourse, if any, the players association has.

Although the joint committee has the authority to discuss virtually any subject related to the safety and welfare of players, it does not appear to have the authority necessary to implement any proposals or remedies it might develop. That is, the committee may make recommendations to the NFLPA, the Management Council, the Commissioner, or an NFL committee, but it does "not have the power to commit or

¹⁸⁵ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 38.

¹⁸⁶ Ibid.

¹⁸⁷ Ibid., p. 39.

¹⁸⁸ Ibid.

bind either" the players association or the Management Council on any issue. ¹⁸⁹ This limitation on its authority may exist because any changes the committee proposes possibly would have to be negotiated pursuant to the collective bargaining process. On the other hand, this limitation might hamper the ability of the NFL and the NFLPA to enact in a timely manner any rule or policy changes necessary to protect the health and safety of the players. Moreover, whereas it appears that the joint committee focuses exclusively on player safety and health, when a recommendation made by the committee is forwarded to one or more of the other parties, it is unclear what other factors, interests, or considerations might be raised by these other parties when discussing the committee's recommendation.

The joint committee also has a role to play if the NFLPA believes that any proposed playing rule changes, which are issued following the NFL's annual meeting, would adversely affect player safety. The process is as follows:

If the NFLPA believes that the adoption of a playing rule change would adversely affect player safety, then within seven days of receiving such notice the NFLPA may call a meeting of the Joint Committee [on Player Safety and Welfare] to be held within one week to discuss such proposed rule change. Within five days after such meeting, if the NFLPA continues to believe that the adoption of a playing rule change would adversely affect player safety, the NFLPA may request an advisory decision by one of the arbitrators designated in Article IX [of the CBA]. A hearing before such arbitrator must be held within seven days of the Joint Committee meeting and the arbitrator must render his decision within one week of the hearing. No such playing rule change will be made by the Clubs until after the arbitrator's advisory decision unless the arbitrator has not rendered his decision within one week of the hearing. The arbitrator's decision will be advisory only, not final and binding. Except as so limited, nothing in this section will impair or limit in any way the right of the Clubs to make any playing rule change whatsoever. 190

While the joint committee's role in this type of situation is relatively minor, the description of the process for addressing rule changes that might adversely affect player safety shows that, ultimately, neither the joint committee, the players association, nor the arbitrator has any capability to modify or rescind a potentially problematic proposed rule change. It is not known how many rule changes, if any, were enacted despite the objections of the NFLPA. Conversely, considering the following excerpt from the CBA, it appears that the NFLPA is not included in the process for proposing new rules and thus cannot propose any rules directed at improving player safety, let alone participate in discussions of rules proposed by the NFL and/or teams: "Immediately following the NFL annual meeting, the NFLPA will be given notice of all proposed playing rule changes, either tentatively adopted by the Clubs or put over for further consideration at a later league meeting." ¹⁹¹

¹⁸⁹ Ibid., p. 38.

¹⁹⁰ Ibid., pp. 38-39.

¹⁹¹ Ibid., p. 38.

Discussion of Selected Issues

Injuries and Financial Considerations

Anecdotal accounts suggest that a player might be concerned that, if he is unable to play because of an injury, his compensation, or his position on the team, might be jeopardized. Faced with one or more possible financial disincentives, a player might choose, then, to conceal an injury and continue to play, thus risking further injury. Moreover, by delaying or not seeking treatment — or even by downplaying the severity of his injury — a player may not receive appropriate, effective medical treatment. The lack of medical treatment, or even just the lack of timely medical care, could have long-term health consequences. Even if a player considers this possibility, the immediate financial incentives of continuing to play might outweigh concerns about possible long-term consequences, particularly since those consequences might not be well known and might be unlikely to occur.

A player does have a financial incentive to report an injury, but this incentive is relatively small. Failure to promptly report an injury to a club physician trainer may result in a fine of up to \$1,500.¹⁹² The financial penalty for failing to report an injury promptly might be less important to a player than the perception, if not the reality, of potential adverse financial consequences related to his willingness to play while injured. If an individual continues to play with an injury, an action that can be facilitated by the use of pain medications, it is possible that he risks aggravating the original injury, or that other parts of his body may be forced to compensate for the injured body part. A possible long-term consequence is that, since the injury is not part of the player's medical records, he might not have documentation he will need as a former player to be eligible for retirement plan disability benefits.

Anecdotal information, in the form of statements by players that have been reported in news articles, suggests that the perception exists among at least some players that, in some cases or situations, a player who reports an injury might be jeopardizing his career. Bob Brudzinski, who was a linebacker for the then-Los Angeles Rams and Miami Dolphins, was quoted as saying

I can't say the owners and coaches didn't care. They wanted to see how tough you are. Anybody can play not injured. They wanted to see if you can play injured. There were a lot of injections and stuff like that. And the other thing is, you didn't want to sit out a game, because there's always somebody behind you who can take your spot. I never thought about concussions, never thought about blowing my knee out. The one thing I wish is that I could remember more. We used our head too much, in the wrong way. 194

Another player, Jim Kelly, former quarterback for the Buffalo Bills, reportedly said

¹⁹² Ibid., p. 19.

¹⁹³ Dustin Dow, "Much Pain, No Gain?" *Cincinnati Enquirer*, July 1, 2007, available at [http://www.factiva.com/].

¹⁹⁴ Brown, "Ex-Players Dealing With Not-So-Glamorous Health Issues."

The game is played with pain.... If you can't play in pain you should be playing golf, like I'm doing now. I think that's the mentality of players. There's a lot at stake. Big contracts, the pressure of losing your job — a lot of things force some guys to do things that maybe they shouldn't do. I know I played in a lot of games that I should not have been playing in, but I did. 195

Referring to the use of painkillers in order to keep playing, an unnamed offensive lineman was quoted in a news article as saying: "When you have 300-pound guys smashing into one another, what do people expect? People just see Sundays, but we hit each other every day.... Ultimately, players take them to stay on the field. Basically you're in a very competitive sport that is cutthroat. There is little tolerance for someone who's not playing." A former linebacker for the San Francisco 49ers, Dan Bunz, reportedly said, "The coaches dangled that carrot — if you're not ready to play, you're going to get cut [....] They just wanted you back on the field. They don't care about you, they just care about the game." 197

The following comments by a former linebacker for the Cleveland Browns, Randy Gardner, suggest that performance incentives (which are discussed below) might contribute to the problem of playing injured: "You have guys who have a lot of incentives based upon playing time, you know? How many catches, maybe, how many tackles — whatever is written into contracts.... And if you don't meet that, you lose out on a lot of money. Guys understand that. They push themselves through the injuries, you know, in order to play and pretty much just to keep their jobs." ¹⁹⁸

Comments by the former director of football operations for the Pittsburgh Steelers, are consistent with the concerns expressed by players. As quoted in a *Washington Post* article, Tom Donahoe said: "Durability becomes a significant factor because there is so much money involved.... If a guy misses five or six games a year, you'll think about whether you want to sign him. And I don't know about all coaches, but many would rather have a guy with less talent who is more dependable than a more talented guy who you don't know when he'll show up." 199

¹⁹⁵ Mike Freeman, "Painkillers, and Addiction, Are Prevalent in N.F.L.," *New York Times*, Apr. 13, 1997, available at [http://query.nytimes.com/gst/fullpage.html?res=950CE7DD1F3CF930A25757C0A961958260].

¹⁹⁶ Ibid. The player who made this comment was not identified in the article.

¹⁹⁷ Ron Kroichick, "Glory Has Its Price: The 1981 49ers, Dan Bunz: Pain, Personal Welfare No Match for Pressure to Play On," *San Francisco Chronicle*, Jan. 21, 2007, available at [http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2007/01/21/SPG0ANLFN11.DTL].

¹⁹⁸ Carl Prine, "Finances Worsen Woes, Critics Say" *Pittsburgh Tribune-Review*, Jan. 9, 2005, available at [http://www.pittsburghlive.com/x/pittsburghtrib/news/specialreports/specialnfl/s_291052.html], p. 4.

¹⁹⁹ Dave Sell, "Football's Pain-Taking Process; Playing Hurt Can Be a Complicated Decision," *Washington Post*, Dec. 8, 1996, p. D1.

Some observers might attribute the players' comments and concerns to the lack of "guaranteed contracts" in the NFL. There is no definition of a "guaranteed contract," but the term is taken to mean that a player who has a guaranteed contract will continue to receive some or all of his compensation even if he is, for example, injured and thus unable to play. The following excerpts from the NFL Player Contract, which permit a team to terminate a player's contract for reasons having to do with, among other things, the player's physical condition and performance, may contribute, at least in part, to the notion that players in the NFL do not have so-called guaranteed contracts:

- 8. PHYSICAL CONDITION. Player represents to Club that he is and will maintain himself in excellent physical condition. Player will undergo a complete physical examination by the Club physician upon Club request, during which physical examination Player agrees to make full and complete disclosure of any physical or mental condition known to him which might impair his performance under this contract and to respond fully and in good faith when questioned by the Club physician about such condition. *If Player fails to establish or maintain his excellent physical condition* to the satisfaction of the Club physician, or make the required full and complete disclosure and good faith responses to the Club physician, *then Club may terminate this contract*.
- 9. INJURY. Unless this contract specifically provides otherwise, if Player is injured in the performance of his services under this contract and promptly reports such injury to the Club physician or trainer, then Player will receive such medical and hospital care during the term of this contract as the Club physician may deem necessary, and will continue to receive his yearly salary for so long, during the season of injury only and for no subsequent period covered by this contract, as Player is physically unable to perform the services required of him by this contract because of such injury. If Player's injury in the performance of his services under this contract results in his death, the unpaid balance of his yearly salary for the season of injury will be paid to his stated beneficiary, or in the absence of a stated beneficiary, to his estate.
- 11. SKILL, PERFORMANCE AND CONDUCT. Player understands that he is competing with other players for a position on Club's roster within the applicable player limits. *If at any time, in the sole judgment of Club, Player's skill or performance has been unsatisfactory* as compared with that of other players competing for positions on Club's roster, or if Player has engaged in personal conduct reasonably judged by club to adversely affect or reflect on Club, *then Club may terminate this contract.* In addition, during the period any salary cap is legally in effect, this contract may be terminated if, in Club's opinion, Player is anticipated to make less of a contribution to Club's ability to compete on the playing field than another player or players whom Club intends to sign or attempts to sign, or another player or players who is or are already on Club's roster, and for whom Club needs room [under the salary cap].²⁰¹

As discussed below, a player may have a "skill guarantee" or an "injury guarantee" written into his contract that protects some or all of his compensation in the event his

²⁰⁰ E.M. Swift, "One Big Headache," Sports Illustrated, Feb. 12, 2007, p. 23.

²⁰¹ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, pp. 252-253. (Italics added to aid in identifying significant text.)

skills decline or he sustains an injury that keeps him from playing, respectively.

The idea of a "guaranteed contract" is, perhaps, an overly broad concept for the NFL, given the different ways in which player compensation may be structured. Generally, the composition and amount of total compensation, and whether all or a portion of the compensation is guaranteed, varies from player contract to player contract. (Generally, a player has an agent who negotiates the terms of his contract with the team. However, a player may negotiate his own contract.) A player's total compensation from the NFL may include, for example, salary, one or more bonuses, and one or more incentives. 202 Incentives are also known as performance bonuses; however, not all bonuses are incentives. One of the better-known bonuses an NFL player may have included in his contract is a signing bonus, which means he will receive a bonus for signing his contract with the team. Some incentives are tied to a team's performance, such as "points scored by offense," "points allowed by defense," and "[number of] sacks allowed." Examples of individual incentives include number of interceptions made, passer rating, and total number of receptions.²⁰⁴ A portion of a player's compensation might be guaranteed, depending upon what was negotiated with the team, but how much is guaranteed, for what reason or reasons, and for which year or years of the contract varies from player to player.

It is difficult to know, then, how much of each player's compensation from the league is guaranteed and how much is not guaranteed. Without this information, and, in particular, data that show how many players, if any, have none, or only a negligible portion, of their NFL compensation guaranteed, it is difficult to know whether, and how many, players could be at risk of adverse financial consequences if they are unable to play because of injuries.²⁰⁵

²⁰² Section 8 of Article XXXVIII of the CBA describes the different types of compensation a player might be entitled to in addition to his salary: "A player will be entitled to receive a signing or reporting bonus, additional salary payments, incentive bonuses and such other provisions as may be negotiated between his Club (with the assistance of the [NFL] Management Council) and the player or his NFLPA-certified agent." (National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 180.)

²⁰³ Ibid., p. 111.

²⁰⁴ Ibid., p. 112. The incentives that are included in a player's contract might serve as an inducement to continue playing with an injury instead of seeking treatment, which might put the player at risk for not meeting the goal(s) in one or more of his incentive clauses. A team physician for the Pittsburgh Steelers, Jim Bradley, reportedly has suggested that "players will beg doctors to get them back into a game so they can make the three catches needed to trigger hundreds of thousands of dollars in incentive clauses in their contracts.... During games, he has signaled trainers to hide an injured player's helmet to prevent a return to the field." (Dan Vergano, "NFL Doctors, Players Face Off Over Painful Choices," *USA Today*, Jan. 31, 2004, available at [http://www.usatoday.com/news/health/2002-01-31-football-medicine.htm].)

²⁰⁵ In the absence of comprehensive data, the long-term financial consequences for players who sustain an injury or injuries, and, as a result, are unable to play, are unknown. The (continued...)

Apparently, however, during the 2007 season, approximately 94% of NFL players had only a portion, if any, of their compensation guaranteed. The NFLPA has noted that, if "the term 'guaranteed' is defined as an individually negotiated clause in a player's contract that assures that he will receive all or most of his salary for the term of the contract, even if he is unable to play due to injury or declining skills, only about 6 per cent of all NFL player contracts are 'guaranteed'." This percentage equates to approximately 102 players for the 2007 season. Looking further back, "from the 1982 through 1992 seasons only *eleven* players had *any* of their base salary guaranteed...." and "[t]he average number of players with guaranteed base salary from 1995 through 2002 [was] 40 per season..." ²⁰⁸

The NFLPA has noted, nevertheless, that signing bonuses are preferable to salary guarantees, and has suggested, generally, that such bonuses equate to guaranteed compensation. Specifically, the players association has stated that "a signing bonus is far more preferable to a salary guarantee" for these reasons: the money is given to the player "up front" (that is, "before he renders his services to the club"); if the club wants some or all of the signing bonus returned (for example, if the player fails to perform), the team "must legally prove its entitlement to a return of any of that money"; and the player can invest the money as soon as he receives it (unlike a salary, which is paid periodically). The NFLPA adds,

It should therefore be clear that signing bonuses, representing a more secure form of compensation than the typical 'guaranteed contracts' in professional baseball and basketball, more than qualify as 'guaranteed' compensation under any definition of that term. In 2006, approximately 52% of all compensation paid to players in the NFL was paid in the form of signing or similar bonuses or

²⁰⁵ (...continued)

actual consequences may differ from players' perceptions, although an analysis performed by the *Pittsburgh Tribune-Review* suggests that a connection might exist between sustaining an injury and having one's salary decreased. The *Tribune-Review*, which analyzed salary and bonus data for 109 individuals who played for the Steelers during the period 1999-2003, found that every game an injured player missed led to "nearly \$73,000 [on average] in wage concessions the next season." (Prine, "Bloody Sundays.")

²⁰⁶ NFL Players Association, "Guaranteed Contracts in Professional Team Sports: How Does the NFL Compare?" NFLPA issue paper, n.d., p. 3.

 $^{^{207}}$ The percentage was calculated using 1,696 as the total number of players (each of the 32 teams has a roster of 53 players).

²⁰⁸ NFL Players Association, "A New Look at Guaranteed Contracts in the NFL," n.d., available at [http://www.nflpa.org/PDFs/Shared/Guaranteed_Contracts.pdf], downloaded Sept. 2007, on file with the author. (Italics in original.)

²⁰⁹ NFL Players Association, "Guaranteed Contracts in Professional Team Sports: How Does the NFL Compare?" p. 4. In this statement, "the term 'signing bonus' includes bonuses which are either labeled as such or are payable 'up front' or with a similar degree of certainty, such as first year roster bonuses, reporting bonuses, or option bonuses." (Ibid., p. 4.)

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guaranteed salary. In a very real sense, it can therefore be said that at least 52% of all compensation in the NFL is, in fact, 'guaranteed' to players.²¹⁰

Although, league-wide, 52% of all compensation in 2006 was virtually "guaranteed," this does not mean that 52% of each player's compensation was "guaranteed."

Variations among players' contracts, specifically signing bonuses, provide a better indication of each player's financial status, and, as the NFLPA has suggested, could indicate what portion of a player's contract is "guaranteed." The NFLPA acknowledges that it "knows better than anyone that not all players can negotiate large signing bonuses or otherwise lucrative contracts." The size of a player's signing bonus might have some bearing on whether and how vulnerable a player might be to internal or external factors inducing him to play when he is injured, recognizing that an individual's decision to play when injured could be the result of a combination of many different factors or considerations.

Signing bonus data are presented in **Tables 8** (1993-1997), **9** (1998-2002), and **10** (2003-2007). Each table shows, for each range of signing bonus amounts, information regarding two groups of players: (1) players who received signing bonuses; and (2) all players, including those who did not receive signing bonuses.

²¹⁰ Ibid. See the preceding footnote for a description of what the NFLPA includes in the term "signing bonus" in this context.

²¹¹ Ibid.

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Table 8. Signing Bonuses Among NFL Players, 1993-1997

	1993		1994		19	1995		1996		1997	
Total Signing Bonus ^a	\$183,413,792		\$2	\$272,809,813 \$460,308		60,308,221	\$563,184,962		\$523,047,173		
Average Signing Bonus		\$308,258		\$271,723		\$364,745		\$480,533		\$436,965	
Total # of Signing Bonuses ^b		595 (40.0%)		1,003 (67.6%)		1,262 (79.4%)		1,172 (73.7%)		1,197 (75.3%)	
Total # of NFL Players ^c		1,484		1,484		1,590 ^d		1,590		1,590	
	% of Players w/ Bonus	% of Total Players ^e									
\$1-\$250,000	73.3	29.4	75.5	51.0	73.5	58.4	70.7	52.1	71.3	53.6	
\$250,001-\$500,000	12.4	5.0	10.1	6.8	9.4	7.5	9.0	6.6	8.9	6.7	
\$500,001-\$750,000	4.2	1.7	3.8	2.6	5.1	4.0	4.0	3.0	5.2	3.9	
\$750,001-\$1,000,000	2.0	0.8	3.7	2.5	2.7	2.1	3.2	2.4	3.8	2.8	
\$1,000,001-\$1,250,000	2.4	0.9	1.2	0.8	1.5	1.2	1.6	1.2	1.0	0.8	
\$1,250,001-\$1,500,000	1.8	0.7	1.5	1.0	1.5	1.2	1.6	1.2	2.1	1.6	
\$1,500,001-\$1,750,000	1.0	0.4	0.5	0.3	0.7	0.6	0.6	0.4	0.7	0.5	
\$1,750,001-\$2,000,000	0.5	0.2	1.2	0.8	1.1	0.8	2.0	1.4	1.6	1.2	
\$2,000,001-\$3,000,000°	1.0	0.4	1.6	1.1	2.6	2.1	3.8	2.8	2.7	2.0	
\$3,000,001-\$4,000,000	0.5	0.2	0.5	0.3	1.0	0.8	1.0	0.8	1.2	0.9	
\$4,000,001-\$5,000,000	0.4	0.1	0.4	0.3	0.4	0.3	1.1	0.8	0.7	0.5	

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	19	93	19	94	19	95	19	96	19	97
\$5,000,001-\$6,000,000	0.1	0.06	0.1	0.06	0.2	0.2	0.7	0.5	0.5	0.4
\$6,000,001-\$7,000,000	0	0	0	0	0.2	0.2	0.5	0.4	0.2	0.1
\$7,000,001-\$8,000,000	0	0	0	0	0.1	0.01	0	0	0.2	0.1
\$8,000,001-\$9,000,000	0	0	0	0	0	0	0	0	0	0
\$9,000,001-\$10,000,000	0	0	0	0	0	0	0	0	0.1	0.06
\$10,000,001 +	0	0	0	0	0.2	0.2	0.1	0.06	0.2	0.1

Source: Information provided by the NFL Players Association to the author on Jan. 8, 2008; as described in table note e, some calculations performed by the author.

- a. The term "signing bonus" "includes bonuses which are either labeled as such or are payable 'up front' or with a similar degree of certainty, such as first year roster bonuses, reporting bonuses, or option bonuses." (NFL Players Association, "Guaranteed Contracts in Professional Team Sports: How Does the NFL Compare?" NFLPA Issue Paper, n.d., p. 4. Information provided by telephone by the NFL Players Association to the author on Jan. 15, 2008.) Although some signing bonuses may be multiyear, each signing bonus in this table is included only in the year in which it was negotiated and agreed to.
- b. Each percentage in this row is the percentage of the total number of players who received a signing bonus.
- c. The total number of players was calculated by multiplying the number of teams by the number of players each team is permitted to have on its regular season and post-season roster, which is 53.
- d. Two expansion teams were added to the league in 1995: the Carolina Panthers and the Jacksonville Jaguars.
- e. The percentage of total players was calculated in this manner: the figure in the column "% of Players w/Bonus" was multiplied by the "Total # of Signing Bonuses." The result of this calculation was rounded and then divided by the "Total # of NFL Players." For example, for the year 1993, .733 (% of Players w/Bonus") was multiplied times 595 ("Total # of Signing Bonuses"). The result was 436.135, which was rounded to 436. Dividing 436 by 1,484 ("Total # of NFL Players") resulted in .2938, or 29.4%.

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Table 9. Signing Bonuses Among NFL Players, 1998-2002

	19	98	19	99	20	00	20	01	20	02
Total Signing Bonus ^a	\$8	\$831,580,214		53,514,150	\$1,052,590,699		\$973,098,236		\$857,847,526	
Average Signing Bonus		\$710,145		\$767,107		\$788,457		\$784,124		\$689,588
Total # of Signing Bonuses ^b		1,171 (73.6%)		1,243 (75.7%)		1,335 (81.3%)		1,241 (75.5%)		1,244 (73.3%)
Total # of NFL Players ^c		1,590		1,643 ^d		1,643		1,643		1,696 ^e
	% of Players w/ Bonus	% of Total Players ^e								
\$1-\$250,000	66.6	49.1	63.0	47.7	62.5	50.8	62.9	47.5	67.8	49.7
\$250,001-\$500,000	8.3	6.1	8.9	6.8	9.4	7.6	9.2	6.9	8.4	6.1
\$500,001-\$750,000	4.7	3.5	3.7	2.8	3.1	2.5	4.4	3.3	3.2	2.4
\$750,001-\$1,000,000	3.2	2.3	4.2	3.2	4.0	3.2	2.6	1.9	2.6	1.9
\$1,000,001-\$1,250,000	1.6	1.2	1.9	1.5	2.2	1.8	1.8	1.3	1.8	1.3
\$1,250,001-\$1,500,000	1.6	1.2	2.5	1.9	2.6	2.1	3.0	2.3	2.4	1.8
\$1,500,001-\$1,750,000	0.9	0.7	2.3	1.8	2.0	1.6	1.0	0.7	1.4	1.0
\$1,750,001-\$2,000,000	1.5	1.1	2.3	1.8	2.0	1.6	2.0	1.5	1.6	1.2
\$2,000,001-\$3,000,000	3.7	2.7	3.7	2.8	4.6	3.7	5.3	4.0	3.9	2.9
\$3,000,001-\$4,000,000	4.0	3.0	2.7	2.1	2.5	2.0	3.3	2.5	2.7	2.7
\$4,000,001-\$5,000,000	1.2	0.9	2.3	1.8	2.1	1.7	1.3	1.0	1.3	0.9

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	19	98	19	99	20	00	20	01	20	02
\$5,000,001-\$6,000,000	0.9	0.7	0.6	0.4	0.7	0.5	1.0	0.7	1.1	0.8
\$6,000,001-\$7,000,000	0.3	0.3	0.6	0.4	0.7	0.5	0.4	0.3	1.0	0.7
\$7,000,001-\$8,000,000	0.8	0.6	0.4	0.3	0.5	0.4	0.5	0.4	0.1	0.06
\$8,000,001-\$9,000,000	0.2	0.1	0.3	0.2	0.2	0.2	0.5	0.4	0.1	0.06
\$9,000,001-\$10,000,000	0.2	0.1	0.2	0.1	0.3	0.2	0.2	0.1	0.4	0.3
\$10,000,001 +	0.4	0.3	0.5	0.4	0.5	0.4	0.5	0.4	0.4	0.3

Source: Information provided by the NFL Players Association to the author on Jan. 8, 2008; as described in table note f, some calculations performed by the author.

- a. The term "signing bonus" "includes bonuses which are either labeled as such or are payable 'up front' or with a similar degree of certainty, such as first year roster bonuses, reporting bonuses, or option bonuses." (NFL Players Association, "Guaranteed Contracts in Professional Team Sports: How Does the NFL Compare?" NFLPA Issue Paper, n.d., p. 4. Information provided by telephone by the NFL Players Association to the author on Jan. 15, 2008.) Although some signing bonuses may be multiyear, each signing bonus in this table is included only in the year in which it was negotiated and agreed to.
- b. Each percentage in this row is the percentage of the total number of players who received a signing bonus.
- c. The total number of players was calculated by multiplying the number of teams by the number of players each team is permitted to have on its regular season and post-season roster, which is 53.
- d. One team was added to the league in 1999 with the re-activation of the Cleveland Browns franchise. (The original Cleveland team was moved, by its owner, to Baltimore in 1995, and became the Baltimore Ravens.)
- e. One expansion team was added to the league in 2002, the Houston Texans.
- f. The percentage of total players was calculated in this manner: the figure in the column "% of Players w/Bonus" was multiplied by the "Total # of Signing Bonuses." The result of this calculation was rounded and then divided by the "Total # of NFL Players." For example, for the year 1998, .666 ("% of Players w/Bonus") was multiplied times 1,171 ("Total # of Signing Bonuses"). The result was 779.886, which was rounded to 780. Dividing 780 by 1,590 ("Total # of NFL Players") resulted in .4906, or 49.1%.

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Table 10. Signing Bonuses Among NFL Players, 2003-2007

	2003		20	04	2005		2006		2007	
Total Signing Bonus ^a	\$833,446,205		\$9	89,681,552	\$775,180,194		\$908,253,709		\$898,656,147	
Average Signing Bonus		\$701,554		\$882,069		\$746,083		\$889,759		\$889,759
Total # of Signing Bonuses ^b		1,188 (70.0%)		1,122 (66.2%)		1,039 (61.3%)		1,069 (63.0%)		1,010 (59.6%)
Total # of NFL Players ^c		1,696		1,696		1,696		1,696		1,696
	% of Players w/ Bonus	% of Total Players ^d								
\$1-\$250,000	65.1	45.6	61.6	41.0	65.0	40.0	62.3	39.3	64.6	38.4
\$250,001-\$500,000	9.7	6.8	9.2	6.1	9.3	5.7	9.4	5.9	9.5	5.7
\$500,001-\$750,000	4.0	2.8	5.0	3.3	3.8	2.3	4.3	2.7	3.8	2.2
\$750,001-\$1,000,000	3.1	2.2	2.9	1.9	4.2	2.6	3.4	2.1	4.0	2.4
\$1,000,001-\$1,250,000	1.8	1.2	2.3	1.5	1.6	1.0	1.9	1.2	1.6	0.9
\$1,250,001-\$1,500,000	2.8	1.9	2.6	1.7	2.6	1.6	2.2	1.4	2.2	1.3
\$1,500,001-\$1,750,000	1.6	1.1	1.2	0.8	1.1	0.6	1.3	0.8	0.6	0.4
\$1,750,001-\$2,000,000	2.2	1.5	2.1	1.4	2.3	1.4	2.6	1.7	1.8	1.1
\$2,000,001-\$3,000,000	3.8	2.6	4.7	3.1	2.9	1.8	4.1	2.6	3.8	2.2
\$3,000,001-\$4,000,000	1.6	1.1	2.6	1.7	2.1	1.3	2.5	1.6	1.9	1.1
\$4,000,001-\$5,000,000	1.4	1.0	1.8	1.2	1.5	0.9	2.3	1.5	1.5	0.9

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	20	03	20	04	20	05	20	06	20	07
\$5,000,001-\$6,000,000	0.9	0.6	1.0	0.6	1.1	0.6	1.0	0.6	1.3	0.8
\$6,000,001-\$7,000,000	0.4	0.3	0.8	0.5	1.2	0.7	0.8	0.5	0.7	0.4
\$7,000,001-\$8,000,000	0.4	0.3	0.7	0.5	0.1	0.05	0.7	0.4	0.6	0.4
\$8,000,001-\$9,000,000	0.2	0.1	0.6	0.4	0.5	0.3	0.3	0.2	0.2	0.1
\$9,000,001-\$10,000,000	0.5	0.4	0.2	0.1	0.2	0.1	0.2	0.1	0.7	0.4
\$10,000,001 +	0.5	0.4	0.7	0.5	0.5	0.3	0.8	0.5	1.5	0.9

Source: Information provided by the NFL Players Association to the author on Jan. 8, 2008; as described in table note d, some calculations performed by the author.

- a. The term "signing bonus" "includes bonuses which are either labeled as such or are payable 'up front' or with a similar degree of certainty, such as first year roster bonuses, reporting bonuses, or option bonuses." (NFL Players Association, "Guaranteed Contracts in Professional Team Sports: How Does the NFL Compare?" NFLPA Issue Paper, n.d., p. 4. Information provided by telephone by the NFL Players Association to the author on Jan. 15, 2008.) Although some signing bonuses may be multiyear, each signing bonus in this table is included only in the year in which it was negotiated and agreed to.
- b. The percentage in this row is the percentage of the total number of players who received a signing bonus.
- c. The total number of players was calculated by multiplying the number of teams by the number of players each team is permitted to have on its regular season and post-season roster, which is 53.
- d. The percentage of total players was calculated in this manner: the figure in the column "% of Players w/Bonus" was multiplied by the "Total # of Signing Bonuses." The result of this calculation was rounded and then divided by the "Total # of NFL Players." For example, for the year 2003, .651 ("% of Players w/Bonus") was multiplied times 1,188 ("Total # of Signing Bonuses"). The result was 773.338, which was rounded to 773. Dividing 773 by 1,696 ("Total # of NFL Players") resulted in .4558, or 45.6%.

The percentage of total players who received a signing bonus each year varied from a low of 40.0% in 1993 to a high of 81.3% in 2000. The largest change between consecutive years was a 27.6 percentage point increase from 1993 (40.0%) to 1994 (67.6%), which might be related to the approval of a new CBA in 1993. For the period 1995-2003, the percentage was at or above 70.0%. However, after reaching 81.3% in 2000, the percentages have declined each year so that, in 2007, 59.6% of total players received a signing bonus, which is a decrease of 21.7 percentage points since 2000. The signing bonus category, the range, and the difference between the lowest and highest percentages are in **Table 11**.

Table 11. Range of Percentage of Total Players Who Received a Signing Bonus, by Signing Bonus Amount

Amount of Signing Bonus	Range of Percentage of Total Players for the Years 1993-2007	Difference in Percentage Points Between Lowest and Highest Percentage
\$1-\$250,000	29.4%-58.4%	29.0
\$250,000-\$500,000	5.0%-7.6%	2.6
\$500,001-\$750,000	1.7%-4.0%	2.3
\$750,001-\$1,000,000	0.8%-3.2%	2.4
\$1,00,001-\$1,250,000	0.8%-1.8%	1.0
\$1,250,001-\$1,500,000	0.7%-2.3%	1.6
\$1,500,001-\$1,750,000	0.3%-1.8%	1.5
\$1,750,001-\$2,000,000	0.2%-1.8%	1.6
\$2,000,001-\$3,000,000	0.4%-4.0%	3.6
\$3,000,001-\$4,000,000	0%-3.0%	3.0
\$4,000,001-\$5,000,000	0.1%-1.8%	1.7
\$5,000,001-\$6,000,000	0.06%-0.8%	0.74
\$6,000,001-\$7,000,000	0%-0.7%	0.7
\$7,000,001-\$8,000,000	0%-0.6%	0.6
\$8,000,001-\$9,000,000	0%-0.4%	0.4
\$9,000,001-\$10,000,000	0%-0.4%	0.4
\$10,000,001+	0%-0.9%	0.9

Sources: Tables 8-10.

The largest percentage of players who received a signing bonus each year received a bonus valued at \$250,000 or less. The percentage of total players who received an amount in this category ranged from 29.4%, in 1993, to 58.4%, in 1995. Except for 1997 and 2000, the percentage steadily declined from 1995 through 2007. The percentage dropped by 20.0 percentage points over this period. Consequently,

in 2007, the percentage (38.4%) is only 9.0 percentage points higher than the 1993 figure (29.4%). The percentages of total players who received other signing bonus amounts experienced much smaller changes over the 15-year period. Thus, **Table** 11 shows that the overall decrease in the percentage of players who received signing bonuses was due primarily to the steady decline in the percentage of players who receive signing bonuses valued at \$250,000 or less.

The nature of the game of football, and, in particular, the risk of injury and how that risk is apportioned between players and teams appears to have some bearing on how compensation is structured. News accounts regarding three players who had sustained injuries — Wayne Chrebet, Matt Birk, and Dan Morgan — and how their respective teams responded to their situations illustrates how risk is allocated between the team and the player. A description of how then-New York Jet Wayne Chrebet's contract was re-structured shows the complexity of one player's contract, and illustrates how a team can protect itself financially. Of particular concern to the team, apparently, was the number of concussions that Chrebet already had sustained; reportedly, he had had at least six concussions by the time he retired several months after the end of the 2005 season. The article on Chrebet's "concussion clause" stated the following:

Chrebet, signed through 2008, agreed to a \$1.3 million pay cut that lowers his base salary this season [2004] to \$1.5 million, according to NFL Players Association documents. The pay cut isn't a surprise, considering Chrebet probably will lose his starting job, but the new contract does include an injuryrelated wrinkle. The Jets got Chrebet to sign a 'split' contract, a complicated deal that would save them from having to pay his entire \$1.5 million salary if he's placed on injured reserve with a concussion. Ordinarily, a player receives his full salary on injured reserve. Clearly, the Jets are concerned that another concussion would end Chrebet's season — and quite likely his career. The 'split' salary, as negotiated by both parties, is \$500,000. It means that, if Chrebet were to land on injured reserve, his salary would drop to \$500,000 from \$1.5 million. Pro-rated over the course of a season, the difference is about \$60,000 per week. The contract states that only a concussion, and no other injury, can trigger the 'split' salary. To sweeten the deal for Chrebet, the Jets guaranteed \$500,000 of the \$1.5 million salary. He receives that amount no matter what, even if he's not on the opening-day roster.²¹³

In 2005, Matt Birk, a center for the Minnesota Vikings, considered how much risk he wanted to take in continuing to play while injured, as recounted in a news article. ²¹⁴ Although he had had three hernia operations and was experiencing chronic

²¹² William C. Rhoden, "A Jet Who Led with His Head, and His Heart," *New York Times*, Sept. 24, 2007, available at [http://www.nytimes.com/glogin?URI=http://www.nytimes.com/2007/09/24/sports/football/24rhoden.html&OQ=_rQ3D1&OP=1744e5c7Q2FlOkAl6_Y Rx__r7l7Q51Q51.lQ51Q27l7blRW_xrRlQ7E__rAyccl7bxQ5D_6kztQ5DrBc].

²¹³ Rich Cimini, "Jets Give Chrebet Concussion Clause," *New York Daily News*, Mar. 31, 2004, available at [http://www.nydailynews.com/archives/sports/2004/03/31/2004-03-31_jets_give_chrebet_concussion.html].

²¹⁴ Joseph Nocera, "The Union That Can't Throw Straight," *New York Times*, Sept. 17, (continued...)

pain, Birk played in most games during the 2004-2005 season. At the beginning of the 2005-2006 season, he asked the team to guarantee his salary for the 2006-2007 season. He offered to play injured — he had a hip injury — during the 2005-2006 season in exchange for guaranteed salary the following season. Reportedly, Birk explained his reasoning as follows:

Playing with pain is part of the game.... But I felt that I had risked my career by playing injured last year [2004], and probably shortened it. And I wasn't willing to do it again unless the team was going to assume some of the risk." So he asked the Vikings to guarantee the \$3.94 million his contract called for him to get next year [2006]. The Vikings declined. On Tuesday, Mr. Birk went under the knife. He's done for the season.²¹⁵

Another player who, reportedly, had his contract restructured because of his team's concern about his history of concussions is Dan Morgan. *The New York Times* article described his situation as follows:

... teams are wary of players with a history of concussions. An example is Carolina Panthers linebacker Dan Morgan — who has sustained at least five concussions but was cleared to continue playing — and faced being cut had he not agreed to restructure his \$2 million roster bonus into payments of \$125,000 for each game he played. Beyond acknowledging the team's concerns about subsequent concussions, the contract gave Mr. Morgan financial incentive not to reveal any concussion for treatment. Mr. Morgan has missed most of this season [2007] with a torn Achilles' tendon, and has declined interview requests by The New York Times. Regarding the restructuring of his contract, Mr. Morgan told The Herald of Rock Hill, S.C., "I didn't have a problem with that, because that's just them protecting themselves."

Without data, it is impossible to know how many players have faced situations similar to Chrebet's, Birk's, or Morgan's; have obtained one or more guarantees in their contracts; or have been unsuccessful in obtaining any type of guarantees.

Andrew Zimbalist, an economics professor at Smith College who has written extensively on sports economics, summarized the situation in the NFL: "'The lack of guaranteed contracts is a natural outcome of football players getting hurt'."²¹⁷ In a similar vein, the NFL Players Association offered this explanation for "no-cut" contracts (that is, contracts that do not include any guarantees):

There's no argument that no-cut contracts in the NFL have been a rarity. For a lot of reasons. Mainly, owners just said "No." That's the way "Things had always been" and traditionally owners held virtually all of the leverage in contract negotiations. That meant that players, who rarely — if ever — had a

²¹⁴ (...continued)

^{2005,} p. C1.

²¹⁵ Ibid.

²¹⁶ Alan Schwarz, "For Jets, Silence on Concussions Signals Unease," *New York Times*, Dec. 22, 2007, p. A20.

²¹⁷ Nocera, "The Union That Can't Throw Straight."

viable alternative if they wanted to have a pro football career, were forced to sign a series of one year non-guaranteed contracts. The NFL was "unique," owners argued, because injury rates to players (who, ironically took all the risks) were so high that there was no desire to have [to] keep on paying players no longer in the league.²¹⁸

If injury risk were re-allocated and the compensation structure were altered accordingly, players might be less likely to play with injuries, which would benefit them immediately, and might also positively affect their long-term health. On the other hand, NFL teams might be adversely affected if they were required to bear more of the risk related to injuries than they do presently. A team cannot pay its players more than the NFL-established salary cap each year. ²¹⁹ The existence of a salary cap means that a team would be unable to hire and pay additional players to play in place of injured players while it continues to pay the salaries of the injured players. A related problem is that a team may be unwilling or unable financially to pay the salaries of more than 53 players (a team can have only 53 players on its regular season and postseason rosters). The NFLPA describes this dilemma for teams as follows:

In the NFL, the salary cap rules require that any salary paid in a given year must count against the cap for that year even if the player is no longer playing. If a team has a large number of guaranteed contracts, a rash of injuries to players covered by those contracts could cause severe cap problems for the team and diminish its ability to compete with healthy players on the field.²²⁰

A journalist for *The New York Times* explains further how "guaranteed contracts" could adversely affect a team's ability to maintain a competitive team:

... there are seasons when dozens of players on one roster will miss at least some games because of injury. If football teams had to pay every player whose abilities were diminished as a result of injury, or had to continue paying a player who had suffered a career-ending injury, there is no way they'd be able to stay

²¹⁸ NFL Players Association, "A New Look at Guaranteed Contracts in the NFL." A related issue is the length of contracts: "Fans often read about multiyear deals, but NFL compensation packages are really a series of one-year contracts. Because of career-ending injuries, players increasingly rely on signing bonuses struck at the beginning of the contract and performance incentives after they take the field. Signing bonuses now constitute half of a player's take-home pay, according to the National Football League Player's Association." (Prine, "Bloody Sundays.") Reportedly, the rationale offered by an employee of the NFL for one-year contracts is as follows: "The NFL is a competitive sports league We put the world's best athletes on the field, so it's a competitive business by its very nature. Let's say a team gave someone a long-term contract. What's the player's incentive to compete? You must have an incentive to get out there and compete at the highest level, or you won't have the competitive excellence that we have in the NFL." (Ibid.)

The "salary cap" is the "absolute maximum amount of Salary that each Club may pay or be obligated to pay" its players each year. (National Football League and the NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 7.)

²²⁰ NFL Players Association, "Guaranteed Contracts in Professional Team Sports: How Does the NFL Compare?" p. 3.

within the [salary] cap. There would be too much "dead money" going to players who weren't playing.²²¹

Combining the salary cap with so-called guaranteed contracts possibly could undermine a team's ability to field a competitive team, which, in turn, might affect the team's revenues.

There may be a particular group of players who are especially vulnerable to choosing to play while injured, because of the way risk is allocated between the team and the players. Framed as a question, are the players who are less likely to have guarantees (or to have large guarantees) included in their contracts also the players who are more likely to be cut from the team? For some positions on a team, there are two, three, or possibly four individuals who can play a particular position. After the starter (the player who, generally, is the best at that position), the other players are listed on the depth chart, in descending order, so that the individual who is number four on the depth chart is possibly the least experienced, or least skilled, player at that position. Players who are number three or number four on the depth chart for their respective positions might feel pressured to play when injured in the hope of moving up the depth chart, or not being cut from the team following the end of the season.²²² Since these players, generally, are the least skilled or least experienced on the team, it seems possible that they are less likely than players who are ahead of them on the depth chart to have guarantees written into in their contracts. Tiki Barber, upon retiring from the New York Giants, reportedly acknowledged that this might be a problem: "Barber was quick to point out that he didn't start to ponder such things [the fact that he was no longer able to recover as quickly after games as he had in the past] until after he was an established star. He said a player trying to make a team, seize a role and earn a payday almost certainly isn't thinking about his long-term health."223

Selected Challenges for Some Retired Players

Clearly, some former players are very successful after their careers have ended. Among the most well-known, by virtue of their success as players and their post-NFL careers as sports broadcasters, are, for example, Terry Bradshaw, Boomer Esiason, Howie Long, Dan Marino, and Phil Simms.²²⁴ Other former players may, for a variety of reasons, experience very different circumstances, as described here:

²²¹ Nocera, "The Union That Can't Throw Straight," p. C1.

²²² Here is another description of what might occur: "NFL depth charts are malleable. Job security is minimal. A player goes down in a practice or a game and is quickly replaced within the next-man-up framework. Many coaches systematically ensure that injured players are out of view of the rest of the team, rehabilitating out of sight and, hopefully, out of mind." (Paul Kuharsky, "Players Sacrifice Health for Game," *Tennessean.com*, Dec. 13, 2007, available at [http://ashlandcitytimes.com/apps/pbcs.dll/article?AID=/20071213/SPORTS01/712130408/1001/NEWS].)

²²³ Ibid.

²²⁴ CBS, "CBS Sports Team," available at [http://sportsline.com/cbssports/team]; Fox Sports, "2007 NFL Schedule on Fox," available at [http://msn.foxsports.com/nfl/story/6671136].

While ex-NFL players can always seek employment in other professional football leagues, such as the Canadian Football League or the Arena Football League, salaries for players in those leagues usually pale in comparison to NFL salaries. Thus, for most NFL players, when their NFL career ends, so too does their professional football career. So instead of continuing a professional football career, many ex-NFL players gravitate toward positions in coaching, scouting, finance, sales or real estate, all of which can offer a good wage by most standards, but typically not by NFL standards. Other ex-NFL players lack the education, skills, or life experience to obtain continuous employment outside of football. In short, life in the NFL may be good, but it's usually very short, and the vast majority of ex-NFL players are headed for lives more akin to those of their fans than of their star teammates.²²⁵

For some retired players, then, finding gainful employment might be relatively difficult. The lack of gainful or continuous employment could be particularly problematic for a retiree who has chronic health problems or one or more disabilities. In addition to financial remuneration, having a job, generally, provides access to health insurance or some other type of health care plan or program. If a retired player is employed by a company that does not provide medical benefits, however, it may be difficult and costly for him to obtain his own health insurance, depending upon the injuries he sustained as a player. As reported by a journalist, Joe Montana, former quarterback of the San Francisco 49ers, needed health insurance upon retiring from the NFL. The lowest estimate he received was \$106,000 per year, because he was considered to be in a high-risk group. 226 Kansas City Chiefs' guard Kyle Turley reportedly has posed the following question: "How am I going to go to an insurance company and say, 'I'm overweight and have all kinds of injuries and now I've got to pay for insurance for the rest of my life'?"227 According to another news article, Miki Yaras-Davis, director of the NFLPA's benefits department, suggested that "most players never make enough over their careers to afford out-of-pocket costs for longterm conditions, and very few insurance carriers will treat gridiron [football] ailments...."228

Another aspect of the financial-medical relationship is that an individual who has one or more chronic health problems or disabilities (as interpreted broadly), might not be able to get or keep a job. The lack of steady employment might decrease the probability that an individual has the resources necessary to obtain health care.

²²⁵ Michael McCann, "NFL Retirement System Not As Bad, or Good, As Argued, *SI.com*, Sept. 18, 2007, available at [http://sportsillustrated.cnn.com/2007/writers/michael_mccann/09/18/hearings/index.html].

²²⁶ Charles Chandler, "Ex-Players Say NFL Neglects Retirees; Hall of Famers: League, Union Leader Fall Short in Providing Benefits," *Charlotte Observer*, June 4, 2007, available at [http://www.factiva.com/].

²²⁷ Les Carpenter, "Split on NFL Union's Effectiveness Lingers," *Washington Post*, Jan. 28, 2008, p. E5.

²²⁸ Prine, "Finances Worsen Woes, Critics Say."

A former player's size — that is, the combination of his height and weight — might lead to difficulties in finding nursing home care. Eleanor Perfetto, the wife of former San Diego Charger Ralph Wenzel, had trouble finding a facility that would take her husband. Wenzel suffers from Alzheimer's-type dementia, and "victims of Alzheimer's-type diseases occasionally become violent, and former football players of his size (6 feet 2 and 215 pounds) are difficult for staff members to subdue. 'These facilities are used to older people who are fairly decrepit — who have strokes or blindness or use a walker, that sort of thing,' Dr. Perfetto said."²²⁹ While the 88 Plan will help former players with dementia and their families pay for their care, Dr. Perfetto's comments suggest that cost may be only part of the challenge in obtaining appropriate health care for players with certain types of diseases.

Total and Permanent (T&P) Disability Benefit

While former players may be concerned about several of the different benefits available to them, the T&P disability benefit seems to be particularly contentious. At congressional hearings in 2007 and in news articles, several former players recounted their experiences in attempting to obtain T&P benefits. The following account about Dave Pear, a former player for the Oakland Raiders and Tampa Bay Buccaneers, appeared in the *Washington Post Magazine*:

Since football, he has undergone seven spinal surgeries, including a 1984 operation to fuse a disk in his neck. He had his most recent spinal surgery last April [2007], when doctors fused two herniated disks in his back. Not unexpectedly, the four screws holding the disks together have left Pear with postoperative discomfort, and at this moment he is experiencing a new throbbing in his right hip. His doctors have said that at some point he'll need two new hips.... At 54, he shuffles like an ailing 80 year-old man. He suffers from chronic fatigue that leaves him falling asleep without warning on most mornings and afternoons....

Off and on for the past quarter-century, [Pear] has been unsuccessfully pressing the NFL for disability benefits that he believes have been unjustly denied him by the league's retirement board. His monthly NFL pension is \$606, but he estimates that he often spends about \$1,000 alone out-of-pocket on medication.... In 1995, he believed his working days were running out. He applied for the league's total and permanent disability benefit with the retirement board. The doctor commissioned by the board to assess his condition portrayed Pear as a man whose physical ailments left him able to do little. Presented with evidence that included reports on Pear's acute fatigue, the doctor said that Pear would require a job that granted him "frequent rest breaks." He would also need, the doctor added, to be limited to sedentary work. Pear should not stand for lengthy periods, should not bend and could not be expected to lift anything more than 15 pounds, the doctor wrote.... The six-man board ... rejected his claim. Three years later, eager to put his hands on cash wherever he could find it, Pear filed for his early retirement pension from the league at the minimum age of 45 and started collecting \$484 a month initially. The small benefit came to Pear's

²²⁹ Alan Schwarz, "Wives United by Husbands' Post-N.F.L. Trauma," *New York Times*, Mar. 14, 2007, p. C15.

savings account at a severe cost: In accepting it, he sacrificed any claim to a disability payment forever, according to the rules of the retirement board plan.²³⁰

The following is the NFLPA's account of Pear's efforts to obtain disability benefits:

Mr. Pear played professional football in the NFL from 1975-1980.... Mr. Pear applied for LOD benefits in 1983. At that time, the Retirement Board was required to determine that the player's injury caused him to leave football before it could grant LOD benefits. After evaluating the report of the neutral physician who examined Mr. Pear, the three player trustees [on the Retirement Board] wanted to award Mr. Pear the LOD benefits, but the three management trustees refused to do so. As a result of this deadlock, the Board sent the issue to an arbitrator, who ultimately ruled that the injury did not cause Mr. Pear to leave football.... Mr. Pear applied for T&P benefits in 1995. The [Retirement] Plan doctor who examined Mr. Pear determined that he could work. The [Retirement] Board therefore concluded that Mr. Pear did not qualify for T&P disability benefits.²³¹

When the T&P disability benefit was established, only two categories of benefits, "active football" and "active nonfootball," were included. The "football degenerative" and "inactive categories" were added in 1993. An individual does not have to be vested to receive "active football" or "active nonfootball" T&P benefits, but he must be vested to receive "football degenerative" and "inactive benefits." The four benefit categories, including the amount of monthly payment, are as follow:

- Active football. The monthly benefit will not be less than \$4,000 if the disability or disabilities arise out of NFL football activities, or arise while the player is an active player, and otherwise cause the player to be totally and permanently disabled "shortly after" the disability or disabilities first arise.²³³
- Active nonfootball. The monthly benefit will not be less than \$4,000 if the disability or disabilities do not result from NFL football activities, but do arise while the player is an active player, and cause the player to be totally and permanently disabled "shortly after" the disabilities first arise.
- Football degenerative. The monthly benefit will not be less than \$4,000 if the disability or disabilities arise out of NFL football activities and result in T&P disability before 15 years after the end of the player's last credited season.

²³⁰ Michael Leahy, "The Pain Game," Washington Post Magazine, Feb. 3, 2008, pp. 10, 23.

²³¹NFL Players Association, "NFLPA White Paper," pp. 14-15. As a result of the collective bargaining process for the 1993 CBA, the requirement for the LOD disability benefit that a player's injury must have forced him to retire was eliminated from the retirement plan. (Ibid., p. 15.)

²³² Letter from Upshaw to Reps. Convers, Smith, Sanchez, and Cannon, p. 5.

²³³ See **Table 4**, note o. for an explanation of "shortly after."

• Inactive. The monthly benefit will not be less than \$1,500 (\$1,750 for applications received on or after April 1, 2007) if the T&P disability arises from other than NFL football activities while the player is a vested inactive player, or the disability or disabilities arise(s) out of NFL football activities and result(s) in total and permanent disability 15 or more years after the end of the player's last credited season, whichever is later.²³⁴

Individuals who receive active T&P benefits in the "active football," "active nonfootball," or "football degenerative" categories automatically qualify for NFL Player Supplemental Disability Plan benefits. Table 12 shows the amounts of payments for each category of T&P benefit. The NFL and the NFLPA announced on February 29, 2008, that "the minimum benefit post-career" for "non-football 'total and permanent' disability" had doubled from "\$20,000 to \$40,000 per year for retired players who become disabled unrelated to football," which, apparently, is a reference to "inactive" benefits. However, because details involving this change are not available yet, **Table 12** does not incorporate this change.

Table 12. Total and Permanent Disability Payments by Category

Category	T&P Disability Benefit Amount	Supplemental Disability Plan Benefit Amount	Total	
Active Football				
Monthly	\$4,000	\$14,670	\$18,670	
Annually	\$48,000	\$176,040	\$224,040	
Active Nonfootball				
Monthly	\$4,000	\$7,167	\$11,167	
Annually	\$48,000	\$86,004	\$134,004	
Football Degenerative				
Monthly	\$4,000	\$5,167	\$9,167	
Annually	\$48,000	\$62,004	\$110,004	

²³⁴ Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 20.

²³⁵ Bert Bell/Pete Rozelle NFL Player Retirement Plan, Summary Plan Description, Apr. 2005, p. 15.

²³⁶ National Football League and NFL Players Association, "NFL and NFL Players Association Expand Disability Benefits Program for Retired Players," p. 1.

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Category	T&P Disability Benefit Amount	Supplemental Disability Plan Benefit Amount	Total
Inactive			
Monthly	\$1,500 ^a	0	\$1,500
	\$1,750 ^b	0	\$1,750
Annually	\$18,000 ^a	0	\$18,000
	\$21,000 ^b	0	\$21,000

Sources: National Football League and NFL Players Association, NFL Collective Bargaining Agreement, 2006-2012, Mar. 8, 2006; Bert Bell/Pete Rozelle NFL Player Retirement Plan, Apr. 1, 2001.

- a. This amount is for players who applied for T&P benefits prior to Apr. 1, 2007.
- b. This amount is for players who applied on or apply after Apr. 1, 2007 for T&P benefits.

An active player who sustains an injury that results in a T&P disability receives the largest annual payment, \$224,040. Comparing the latter three categories with this category ("active football") shows that the "active nonfootball" total annual amount equates to 60% of the "active football" benefit total annual amount; "football degenerative" equates to 49%; and "inactive" equates to 8% (\$18,000) and 9% (\$21,000). The size of the payment for the "inactive" category, when compared to the size of the payments for the other three categories, and the threshold for distinguishing between a "degenerative football" disability and an "inactive" disability (which is discussed below), might contribute to the contentious nature of disagreements between retirees, on the one hand, and the NFL, the NFL Players Association, and the Plan Office, on the other hand.

As **Table 12** shows, the benefit amount decreases if the disability is not related to football, and whether a disability is related to football is determined by the amount of time that has passed since retirement from the NFL. In the following explanation of how T&P benefits are structured, the NFLPA essentially confirms that this is the methodology for determining the size of benefit for each category:

The criteria for all of these T&P benefits [the four categories] were forged in collective bargaining. Which category applies in a specific case generally depends on (1) the cause of the disability and (2) the length of time between a player's NFL career and his inability to work. In the view of the NFLPA, it is appropriate for the benefit to be greater where NFL football was the cause and it is appropriate that the payment amount may depend in part on the length of time between the player's NFL career and his inability to work. ²³⁷

This explanation raises a few questions. For example, does scholarly literature indicate that total and permanent disabilities caused by injuries peculiar to playing professional football manifest themselves within a certain time frame? Specifically, is the time frame selected by the NFL and the NFLPA — 15 years — supported by

²³⁷ Letter from Upshaw to Reps. Convers, Smith, Sanchez, and Cannon, p. 18.

scholarly literature? Additionally, do some types of disabilities appear later than others?

The threshold (that is, time frame) for determining whether a player's disability can be classified as "football degenerative" instead of "inactive" was changed in 2006 for applications received on or after September 1, 2006. **Table 13** shows the relevant language prior to the 2006 amendment — which still applies to applications received prior to September 1, 2006 — and the current (post-amendment) language, which applies to applications received on or after September 1, 2006. The key difference between the two versions, as shown below, is that the time threshold, which is used to determine whether a player who is otherwise eligible for T&P benefits receives the "football degenerative" benefit, has changed.

Table 13. Selected Criteria for Football Degenerative and Inactive Categories

Retirement PlanVerison	Football Degenerative	Inactive
Prior to 2006 Amendment ^a	"(c)The monthly benefit will not be less than \$4,000 if the disability or disabilities arise out of NFL football activities and results in T&P disability before age 45 or 12 years after the end of the player's last credited season, whichever is later."	"(d) Inactive: monthly benefit will not be less than \$1,500 if the T&P disability arises from other than NFL football activities while the player is a vested inactive player, or the disability or disabilities arises out of NFL football activities and results in total and permanent disability after age 45 or 12 years after the end of the player's last credited season, whichever is later."
2006 Amendment ^b	"(c) Football degenerative: monthly benefit will not be less than \$4,000 if the disability or disabilities arise out of NFL football activities and results in T&P disability before 15 years after the end of the player's last credited season."	"(d) Inactive: monthly benefit will not be less than \$1,500 [or \$1,750 for individuals who applied on or after April 1, 2007] if the T&P disability arises from other than NFL football activities while the player is a vested inactive player, or the disability or disabilities arises out of NFL football activities and results in total and permanent disability 15 or more years after the end of the player's last credited

Retirement PlanVerison	Football Degenerative	Inactive
		season, whichever is later."

Sources: Bert Bell/Pete Rozelle NFL Player Retirement Plan, Apr. 1, 2001; "Bert Bell/Pete Rozelle NFL Player Retirement Plan, Amendment," amendment to Sec. 5.1(c), signed Sept. 12, 2006; "Bert Bell/Pete Rozelle NFL Player Retirement Plan, Amendment," amendment to Sec. 5.1(d), signed Oct. 4, 2006.

- a. The language in this row applies to applications received prior to Sept. 1, 2006.
- b. The language in this row applies to applications received on or after Sept. 1, 2006.

Table 14 shows how the change in the threshold will affect players, depending upon the age at which they retire, who file for T&P disability benefits on or after September 1, 2006.

Table 14. Effect of 15-Year Threshold on Eligibility for "Football Degenerative" Benefits

Age at Which Player	Latest Age at Which Player Can Receive "Football Degenerative" Benefits	
Retires	Prior to 2006 Amendment	2006 Amendment
23ª	45	38
25	45	40
30	45	45
35	47	50
40	52	55
45	57	60
50	62	65

Sources: Table developed by the author using the following information: *Bert Bell/Pete Rozelle NFL Player Retirement Plan*, Apr. 1, 2001; "Bert Bell/Pete Rozelle NFL Player Retirement Plan, Amendment," amendment to Sec. 5.1(c), signed Sept. 12, 2006; "Bert Bell/Pete Rozelle NFL Player Retirement Plan, Amendment," amendment to Sec. 5.1(d), signed Oct. 4, 2006.

a. This is most likely the youngest age at which a player could retire and be vested. A player must have three credited seasons to be vested, and it is assumed that no one younger than 20 enters the NFL. Pursuant to the CBA, an individual shall not be eligible for the draft "until three regular NFL seasons have begun and ended following either his graduation from high school or graduation of the class with which he entered high school, whichever is earlier. For example, if a player graduated from high school in December 2006, he would not otherwise be eligible for selection, until the 2010 Draft." (National Football League and NFL Players Association, NFL Collective Bargaining Agreement, 2006-2012, Mar. 8, 2006, p. 46.)

This table shows that the change in criteria will affect differently players younger than age 30 and players older than age 30 at the time of retirement. For players who are younger than 30 when they retire, their disabilities, if any, will need to surface at a younger age than under the previous criteria for them to be eligible for the "football degenerative" benefit. Players who retire at age 31 or older will have an additional three years, compared to the previous criteria, in which their disabilities may surface for them to be eligible for the "football degenerative" category. The implications of this change in criteria for players who retire before they reach age 30 are unknown. As noted above, the length of an average career is $3\frac{1}{2}$ seasons, so a significant number of players might retire before age 30. Accordingly, players who have relatively short careers probably sustain fewer injuries than their peers who play for 10 or 15 years.

Applications for disability benefits are initially considered by the Disability Initial Claims Committee (DICC). Subsequently, an applicant may have an application reconsidered by the Retirement Board. (29 CFR §2560.503-1(h)(3)(ii) and (4) require a disability plan to have a mechanism for an applicant to appeal an adverse benefit determination, and stipulate that neither the individual who made the adverse determination, nor anyone subordinate to this individual, can hear the appeal.) On its review, the Board is not bound by the evidence presented to the DICC or its findings, but rather has broad discretion as to what it may take into account, including evidence not previously presented. Decisions of the Board may be appealed to federal courts.

Overall, from July 1, 1993, through June 26, 2007, 1,052 individuals applied for LOD or T&P disability benefits: 428 applications were approved; 576 were denied; and 48 are pending. The approval rate, which does not include the cases that are pending, is 42%. The following series of statements shows the status of applications at each step of the process.

- 1,052 applications submitted for disability benefits.
 - 358 (34%) applications approved.
 - 675 (64%) applications denied.
 - 19 (2%) applications are pending.
- 223 (33% of 675) applications denied at the initial stage were appealed.
 - 69 (31%) approved on appeal.
 - 132 (60%) denied on appeal.
 - 22 (10%) appeals are pending.
- 32 (24% of 132) applicants whose appeals were denied filed a lawsuit.
 - 1 (3%) lawsuit resulted in a reversal of the Retirement Board's decision.

²³⁸ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, pp. 9-10.

- 24 (75%) lawsuits resulted in the Retirement Board's decisions being upheld.
- 7 (22%) lawsuits are pending.²³⁹

This tally shows that of the cases it decided, the DICC's approval rate was a little over 34%. The Retirement Board's approval rate of the cases it reviewed following DICC consideration was similar, at 31%. The opportunity for Retirement Board review resulted in a greater overall approval rate of about 42% of applications filed. On the other hand, were the Retirement Board alone to have considered applications, it is not certain that the overall approval rate would have been lower than 42%, or if the approval rate might be equal to or even exceeding the 42% rate.

The reasons applications are denied, which are not publicly available, might shed some light on why applicants decide not to appeal, or otherwise challenge, adverse decisions. Some applicants may have missed a deadline, not been able to provide satisfactory documentation to the Disability Initial Claims Committee (DICC), or applied for T&P benefits while already receiving a retirement plan pension (a player who is receiving a pension is not eligible for disability benefits). Information on the reasons for denial possibly could be useful in identifying processes, policies, or guidelines that could be improved. Information on the reasons for denial, particularly if made available to former players (if not to the public as well), could provide some transparency and possibly facilitate accountability.

Table 15 shows how many former players receive, or have received, T&P benefits as of a single day. The latter group includes players who, upon reaching age 55, had their T&P benefits automatically converted to pension payments, with no reduction in the amount of money they receive. The data in **Table 15** are current as of a single day, October 23, 2007.

Table 15. Number of Players Who Are Receiving or Have Received T&P Benefits, as of October 23, 2007

T&P Disability Category	Number and Percentage of Players Receiving T&P Benefits as of October 23, 2007 ^a	Number and Percentage of Players Who Are Age 55 or Older and Who Previously Received T&P Benefits ^b	Total
Active	6	(3%)	8
Football	(4%)		(4%)
Active	9 (6%)	3	12
Nonfootball		(4%)	(5%)
Football	91	21	112
Degenerative	(60%)	(30%)	(50%)

²³⁹ Ibid.

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T&P Disability Category	Number and Percentage of Players Receiving T&P Benefits as of October 23, 2007 ^a	Number and Percentage of Players Who Are Age 55 or Older and Who Previously Received T&P Benefits ^b	Total
Inactive	48 (31%)	44 (63%)	92 (41%)
Total	154	70	224

Source: Letter from Eugene Upshaw, Executive Director, NFL Players Association, to Reps. John Conyers, Jr., Lamar S. Smith, Linda T. Sanchez, and Christopher B. Cannon, Nov. 5, 2007, pp. 6-7.

According to **Table 15**, eight players receive the highest payment available (\$224,040). Moving on to "active nonfootball," 12 former players receive payments that equate to 60% of the highest payment; 112 players in the "football degenerative" category receive payments that are 49% of the highest amount; and 92 players in "inactive" category receive 8% or 9% of the highest amount. Comparing the total number of players who are younger than age 55 with the total number of players who are age 55 or older shows that more than twice as many players receiving T&P benefits are under age 55. **Table 15** also shows that the percentages of players receiving "active football" and "active nonfootball" benefits are similar. A significant difference between the two age groups is evident in the percentages of players who receive "football degenerative" and "inactive" benefits: 60% of the players younger than 55 receive "football degenerative" benefits while only 30% of players older than 55 receive the same type of benefit. The percentages are reversed for "inactive benefits." It is not clear why this difference exists. It may be due, for example, to changes in the benefit plan over the years. As noted above, the benefit plan initially included only two types of T&P benefits.

A comparison between active players and former players shows that only 9% (active football and active nonfootball) of the T&P disabilities occurred when an individual was in the NFL. Conversely, the data suggest that most T&P disabilities — 91% — surface after players have retired and been out of the NFL more than six months.

The league and the players association have taken steps designed to improve the disability application process. In December 2007, the NFL announced that the organizations had agreed on a series of improvements involving disability benefits, including providing prescription drug cards to retired players that will permit them to buy prescription medications at a discount.²⁴⁰ The changes are as follow:

a. This column includes former players who are age 54 or younger.

b. Disability benefits are converted to retirement benefits at age 55. The amount of the benefit does not change when the conversion occurs.

²⁴⁰ National Football League, "Improvements Made to Disability Plan Procedures," news release, Dec. 12, 2007.

- 1. Medical Director The plan will retain a medical director to consult with the two-person initial claims committee and, as needed, with the retirement board to assist in resolving claims. It is expected that this will reduce the number of initial denials at the claims committee level, expediting both initial approvals and the processing of appeals. In addition, the medical director can help ensure that standards are consistently applied, that reports are prepared in a timely basis, and otherwise monitor the performance of neutral physicians.
- 2. Physician Panels The plan will establish a series of physician "panels" or "teams," consisting of doctors with experience in orthopedic and other practices. These teams will be located in areas where there is the largest concentration of retired players, including in Arizona, California, Florida and Texas, as well as in other major metropolitan areas. This change will reduce the trips required of people needing to be examined by doctors in different specialties.
- 3. Claims Specialist The plan will provide a specialist to receive calls from applicants via a toll-free number. This specialist will assist in preparing applications and advise applicants on the information that is required. The completed application will be sent to the applicant for review, verification and signature. The 45-day review period will begin once the signed application is returned. This service will make it more likely that applications are completed correctly the first time and thus reduce the processing time.
- 4. Expedited Email Appeals The retirement board will, whenever possible, decide appeals via email ballots. This will allow for faster decisions on many appeals and will avoid requiring applicants to wait for the next scheduled meeting of the retirement board.
- 5. Extending Review Period The plan will reduce the number and frequency of continuation reviews for those applicants receiving total and permanent disability benefits by extending the current three-year maximum to at least five years. Any three trustees may require a continuation review more frequently, although not more frequently than annually, if they decide there is reason to do so.²⁴¹

Furthermore, the NFL and the NFLPA have agreed that any eligible former player who is receiving Social Security disability benefits will be granted disability benefits automatically and will not have to be examined by a retirement plan doctor. Other changes to T&P disability benefits may be found in **Table 4**.

Conducting a program evaluation of the T&P disability benefit plan, which would include an examination of the outcomes and unintended consequences, if any, of these changes, could aid in establishing and maintaining an efficient, effective, and responsive disability plan and application process. Sharing the results of the study with all interested parties, including, for example, the NFL, NFLPA, former players, and active players, could promote transparency and accountability.

²⁴¹ Ibid.

²⁴² NFL Players Association, "NFLPA White Paper," n.d., pp. 5-6.

Is There a Subset of Former Players with Exceptional Needs?

For a variety of reasons, it seems possible that a former player's financial and medical needs might be related to his age. While the usual effects of the aging process can affect a retiree's health and employment situation, there may be additional factors that could affect older retirees. Over the years, improvements and advances have taken place in these areas: playing rules, 243 equipment, and playing surfaces; medical knowledge, procedures, and technologies; and benefits. Therefore, it seems likely that individuals who played 20, 30, and 40 years ago might not have been protected as well as current players; might have received medical care that, while the best available at the time, was not as effective or successful as the care available today; and are not eligible for all of the benefits available to current players. Thus, older players might be a subset with, for the reasons stated here, exceptional financial and medical needs, and their needs exceed the benefits available to them.

Playing rules, protective equipment, and playing surfaces have evolved over the years. For example, until it was prohibited in 1977, a player could use the "head slap" (that is, slap another player on the side of his helmet) to disorient another player. As for protective equipment, the helmet, which, in addition to shoulder pads, is the only piece of protective equipment players are required to wear, has evolved from wool stocking caps (1800s) and leather (1920s) to fiber shell (1934) and plastic (1943-present). Additionally, it was not until the early 1970s that the first safety requirements for football helmets were instituted. Regarding the

²⁴³ Over the years, the NFL has forbade a number of techniques used by players against one another that were deemed dangerous, such as "clothes lining," "spearing," and "cut blocking." See National Football League, "Summary of Penalties," available at [http://www.nfl.com/rulebook/penaltysummaries].

²⁴⁴ U.S. Congress, House Committee on the Judiciary, Subcommittee on Commercial and Administrative Law, "The National Football League's System for Compensating Retired Players: An Uneven Playing Field? statement of Cy Smith, unpublished hearing, 110th Cong., 1st sess., June 26, 2007, p. 4.

²⁴⁵ Alan Schwarz, "Far From Grandpa's Leather, Helmet Absorbs Shock a New Way," *New York Times*, Oct. 27, 2007, p. A10.

Operating Committee on Standards for Athletic Equipment (NOCSAE), was formed in 1969. NOCSAE comprises "representatives from a number of groups which have an interest in athletic equipment. These include manufacturers, reconditioners, athletic trainers, coaches, equipment managers, sports medicine and consumer organizations." (National Operating Committee on Standards for Athletic Equipment, "About NOCSAE," available at [http://www.nocsae.org/about/index.html].) Improvements in helmet technology continue. A new helmet, the Xenith X1, has been developed that "features 18 black, thermoplastic shock absorbers filled with air that ... can accept a wide range of forces and still moderate the sudden jarring of the head that causes concussion. Morever, laboratory tests have shown that the disks can withstand hundreds of impacts without any notable degradation in performance, a longtime drawback of helmets' traditional foam. Dr. Robert Cantu of Brigham and Women's Hospital in Boston, one of the nation's leading experts in concussion management, reportedly called it 'the greatest advance in helmet design in at (continued...)

playing surface in NFL stadiums, the type or types of artificial turf used in the past were found to contribute to players' injuries. A 1974 study commissioned by the NFL reportedly found that "natural grass was safer to play on than the artificial surfaces then being produced for football." A 1985 *Sports Illustrated* article reported that "[t]he NFLPA found that the average turf injury took longer to heal, that the number of players placed on injured reserve increased by a third and that the number of missed games doubled when the injuries occurred on turf." ²⁴⁸

It seems likely, because of ongoing medical research and advances in medical care, procedures, and technologies, that players today receive better medical care than individuals received in the past. The following excerpt from an article summarizes some of the advances that have occurred since the early 1980s:

Arthroscopy. Doctors can now repair knees, shoulders and other joints without making huge incisions. Instead, they use tiny tools snaked via tubes under the skin to perform surgery. In the early 1980s, reconstructing a knee ligament could require a two-foot long incision and a two-hour procedure. Now it may only take a few half-inch ones and only 40 minutes to complete.

Imaging. Players might get daily X-rays to assess the progress of a broken bone. Steelers linebacker Earl Holmes was hurt in the second quarter of one playoff game; doctors had magnetic resonance imaging pictures of his knee by the third quarter.

Year-round training. Players now get nutrition, sports psychology and strength-training advice designed specifically around their injuries and train year-round to prevent them.²⁴⁹

In the following excerpt from a news article, a fullback for the Tennessee Titans plans to rely on improvements the field of medicine for treating his injuries, and notes a difference between his father's experience and his experience with knee surgery:

²⁴⁶ (...continued)

least 30 years'." (Schwarz, "Far From Grandpa's Leather, Helmet Absorbs Shock a New Way," p. A1.)

²⁴⁷ John Underwood, "Just an Awful Toll," *Sports Illustrated*, Aug. 12, 1985, available at [http://www.lexisnexis.com/], p. 48.

²⁴⁸ Ibid. As of 2007, 19 NFL stadiums had grass playing fields, and the remainder had artificial turf, though it seems likely that, because of improvements over the years, the artificial turf installed in stadiums in the 21st century is better than the products that were installed 20 and 30 years ago. (Stadiums of the NFL, "Comparisons," available at [http://www.stadiumsofnfl.com/ comparisons.htm].) According to this source, among the stadiums that have artificial turf, 11 have had FieldTurf installed, and one stadium has a SportExe product. Information about these companies and their products is available at [http://www.fieldturf.com/index.cfm] and [http://www.sportexe.com/], respectively. These companies' websites include descriptions of how their products are designed and constructed.

²⁴⁹ Vergano, "NFL Doctors, Players Face Off Over Painful Choices."

... Casey Cramer said he's thought about the effects of poundings, but he's placing a large degree of faith in medical advances. He remembers how arduous it was for his dad, a former player, to recover from knee surgery 30 years ago. He also remembers being able to walk within hours of his own knee operation. "I feel like the science is getting a lot better," Cramer said. "Surgeries, medicines, and all of those things have improved over the years. I've said jokingly that I'm banking on science to fix my body afterwards, [but] I feel like 20 or 30 years from now, science will be a lot better." 250

Former players who did not have the benefit of the rules, protective equipment, and medical procedures and technologies that are available to today's players also have fewer benefits available to them. As shown in **Table 16**, individuals who played in the NFL prior to 1982 have eight benefits available to them; current players have 14 benefits. While this comparison shows that the number of benefits has increased over the years, it also shows how many and which benefits are not, or were not, available to some former players. For the reasons described above, however, older retirees might have the greatest medical and financial needs.

The NFL and the NFLPA announced, on February 29, 2008, that five additional benefits had been, or would be, established for former players: a joint replacement surgery and rehabilitation program, a screening program for cardiovascular health and obesity, a prostate cancer screening program, discounted rates for assisted living facilities managed by three companies, and a prescription drug card. Additional information regarding these benefits is provided above, but because, for example, eligibility criteria, implementation dates, and other details have not been publicized yet, these benefits are not included in **Table 16**.

At least a few benefits were made retroactive when established or at some later date, which means that a benefit is available to all players, regardless of which year or years they played in the NFL. The 88 Plan is an example of a benefit that is retroactive, and, in 1993, the players known as "pre-59ers" were added to the Bert Bell Pension Plan. The nature of some benefits, however, seems to have precluded making them retroactive. Examples include the Second Career Savings Plan and severance pay.

²⁵⁰ Ibid.

²⁵¹ National Football League and NFL Players Association, "NFL and NFL Players Association Expand Disability Benefits Program for Retired Players," Feb. 29, 2008, pp. 2-3.

Table 16. Benefits Available to Players

If an Individual Played in the NFL During the Following Period:	The Benefits Available to Him Are: ^a
Not later than 1981	88 Plan Cardiovascular Health Program Death Benefits Line of Duty Disability NFL Player Joint Replacement Benefit Plan Retirement Benefits Total and Permanent Disability Benefits Workers' Compensation
1982-1992	88 Plan Cardiovascular Health Program Death Benefits Line of Duty Disability NFL Player Joint Replacement Benefit Plan Retirement Benefits Severance Pay ^b Total and Permanent Disability Benefits Workers' Compensation
1993-1997	88 Plan Cardiovascular Health Program Death Benefits Line of Duty Disability NFL Player Joint Replacement Benefit Plan Retiree Medical ^b Retirement Benefits Second Career Savings Plan ^b Severance Pay Supplemental Disability Plan ^b Total and Permanent Disability Benefits Workers' Compensation
1998-2003	88 Plan Annuity Program ^b Cardiovascular Health Program Death Benefits Line of Duty Disability NFL Player Joint Replacement Benefit Plan Retiree Medical Retirement Benefits Second Career Savings Plan Severance Pay Supplemental Disability Plan Total and Permanent Disability Benefits Workers' Compensation
2004-Present	88 Plan Annuity Program Cardiovascular Health Program ^b

If an Individual Played in the NFL During the Following Period:	The Benefits Available to Him Are: ^a
	Death Benefits Health Reimbursement Account Plan ^b Line of Duty Disability NFL Player Joint Replacement Benefit Plan ^b Retiree Medical Retirement Benefits Second Career Savings Plan Severance Pay Supplemental Disability Plan
	Total and Permanent Disability Benefits Workers' Compensation

Source: Letter from Eugene Upshaw, Executive Director, NFL Players Association, to Reps. John Conyers, Jr., Lamar S. Smith, Linda T. Sanchez, and Christopher B. Cannon, Nov. 5, 2007, p. 20.

- a. A player has to meet the eligibility criteria to receive a benefit.
- b. The benefit was established during this time period. If the benefit is retroactive, it appears in the list for previous time period(s).

In some cases, it is possible that an individual made one or more decisions that, ultimately, resulted in adverse consequences. For example, players are, or have been, able to choose when and how they receive certain benefit payments, but the consequences of some choices can negatively affect the individual's financial status. Examples of such choices are the following:

- Prior to the 1993 CBA, a player could choose to begin receiving his pension at age 45, which is 10 years earlier than the NFL's normal retirement age of 55. By electing to begin his pension 10 years early, the "age-55 benefit is actuarially reduced by more than 50% in this situation, since [the former player] will receive [his] pension for ten more years." This option is no longer available, except to former players who played in at least one season prior to 1993. Despite being warned about the consequences of opting for an early pension, players continue to do so.²⁵²
- Some former players chose a "Social Security Adjustment" form of benefit, "in which the majority of their retirement benefit is paid prior to age 62, with only a token benefit starting at age 62." Electing this option decreases a player's retirement benefits when he

²⁵² NFL Players Association, "NFLPA White Paper," pp. 22-23. As noted above, players who took their NFL pension early "will be offered a new one-time opportunity" in 2008 to apply for T&P disability benefits. (National Football League and NFL Players Association, "NFL and NFL Players Association, "NFL and NFL Players Association Expand Disability Benefits Program for Retired Players," p. 1.)

reaches age 62.²⁵³ "For example, instead of receiving \$271 a month for life beginning at age 45, a player could use this ... option to receive about \$384 a month from age 45 up to age 72, and only \$50 a month thereafter."²⁵⁴

• Beginning with the 1977 CBA, a player was able to choose a lump sum "early payment benefit" (EPB), which was equal to 25% of his pension, one year after retiring from the NFL. As a result, all pension payments he would have received later were reduced by 25%. 255

The 1993 CBA eliminated all three of these options for players who entered the NFL in 1993 or later. According to the plan counsel for the retirement plan, under federal law, these options remain available to players who earned a credited season before 1993.²⁵⁶

In congressional testimony, the plan counsel showed, through the following account of an unnamed former player's circumstances, how a series of decisions can adversely affect an individual's finances:

[He] complains that his retirement benefit is too small, but doesn't mention that he 1) chose to retire at age 45 with a 45% actuarial reduction, 2) elected the social security option providing the lion's share of his pension up front, 3) knew that he would only receive a token pension when he became 62, and 4) was ordered by a divorce court to share his pension with his ex-wife.²⁵⁷

As reported by a journalist, Leroy Kelly, a former running back for the Cleveland Browns, requested that his pension begin at age 45. Consequently, his \$800 monthly payment decreased to \$112 when he began drawing Social Security payments.²⁵⁸ Another former player, Joe DeLamielleure, also chose to take his pension early. Faced with a family financial crisis, the former guard for the Cleveland Browns and Buffalo Bills opted for an early pension, which resulted in a monthly payment of \$992; if he had waited until he reached age 55 (normal retirement age for players), he would have received \$2,200 per month.²⁵⁹ These examples show that a player's

²⁵³ Ibid., p. 23.

²⁵⁴ U.S. Congress, House Committee on the Judiciary, Subcommittee on Commercial and Administrative Law, "The National Football League's System for Compensating Retired Players: An Uneven Playing Field?" statement of Douglas W. Ell, unpublished hearing, 110th Cong., 1st sess., June 26, 2007, p. 6.

²⁵⁵ Ibid.

²⁵⁶ Ibid., p. 8.

²⁵⁷ Ibid., p. 18.

²⁵⁸ Charles Chandler, "Ex-Players Say NFL Neglects Retirees; Hall of Famers: League, Union Leader Fall Short in Providing Benefits," *Charlotte Observer*, June 4, 2007.

²⁵⁹ Ibid.

decisions and personal circumstances (for example, getting a divorce) also might affect the level of benefits that he receives.

What Is Known about Injuries and Possible Long-Term Consequences?

Considering the frequency and extent of football injuries, the potential risk of certain medical conditions (such as excessive weight, cardiovascular disease, and sleep apnea), and the possibility that injuries and medical conditions might have long-term consequences, how much is known about these subjects? Specifically, what do the NFL and the NFLPA know; what are their sources of information; and how do they use the information? The league and the players association have conducted or sponsored, separately as well as jointly, studies and articles on subjects related to players' health, and the NFL has several studies planned or in progress. However, as demonstrated by the following examination of MTBI research, contradictions among the findings of different studies contribute to the challenge of understanding injuries, medical conditions, and their possible long-term consequences.

The following four subsections present scholarly research on the long-term effects of concussions, susceptibility to additional MTBI, and chronic traumatic encephalopathy (CTE). It is beyond the scope of this report to assess the merits and drawbacks of scholarly articles in the field of neurology. Excerpts from articles and peer reviews of articles are included to show the findings and the nature or extent of disagreement among authors. Some disagreements may flow from methodological differences, such as the type of survey instrument used (for example, telephone, mail, or personal interview) or the method used to select study participants.

Several of the articles included here were written by members of the NFL's MTBI Committee. The other articles were written by professionals in the field of neurology or related fields who are not affiliated with the NFL or the NFLPA. Members of the MTBI Committee have published 14 articles in the journal *Neurosurgery*. Within each heading, articles are presented in the order in which they were published. In *Neurosurgery*, peer reviewers' comments on particular articles are published following the articles, and excerpts from each peer reviewer's comments are included with the applicable article.

Studies on Possible Long-Term Effects of MTBI. Although members of the MTBI Committee did not publish an article focused exclusively on the long-term effects of concussions, they did address the issue in an article on neuropsychological testing. In the sixth article of the 14-article series, committee members suggested that multiple MTBIs would not permanently affect an individual. Pellman, et al., wrote the following:

²⁶⁰ A list of these studies and articles is found in **Appendix B**.

²⁶¹ These articles are included in **Appendix B**.

The strong correlation between the results of clinical and neuropsychological evaluations also provides supportive evidence for the position that there is no evidence in this study of widespread permanent or cumulative effects of single or multiple MTBIs in professional football players. In other words, the results of this present study support the authors' previous work, which indicated that there was no evidence of worsening injury or chronic cumulative effects of multiple MTBIs in NFL players. ²⁶²

NFL players did not demonstrate evidence of neurocognitive decline after multiple (three or more) MTBIs or in those players out 7+ days [from the date of the concussion]. The data show that MTBI in this population is characterized by a rapid return of neuropsoychological function in the days after injury.²⁶³

A theme among peer reviewers' comments was that the finding — the evidence does not support a link between single or multiple MTBIs and long-term effects — was questionable. The following are excerpts from peer reviewers' comments:

In addition, I do not believe that this study, with correlation between clinical and neuropsychological evaluation, proves that there are no widespread permanent or cumulative effects of single or multiple MTBI in NFL players. I think that it is premature to conclude that there are no long-term consequences of MTBI in football while players are still active, for many reasons.²⁶⁴

... these results should be interpreted with caution. Further follow-up of players sustaining MTBI is needed to better determine the cumulative effect of multiple concussions. ²⁶⁵

The authors possess a remarkable data set. My strongest impression after reading the article was that the data set was so important that it deserved additional analysis and that a good place to start would be to remove the outliers and see the results. ²⁶⁶

It is specifically recommended that the statement that there are no widespread permanent or cumulative effects of single or multiple MTBIs in professional football players be softened somewhat.²⁶⁷

²⁶² Elliot J. Pellman, et al., "Concussion in Professional Football: Neuropsychological Testing — Part 6," *Neurosurgery*, vol. 55, no. 6, Dec. 2004, p. 1299.

²⁶³ Ibid., p. 1290. As quoted in a news article in the *Wall Street Journal*, Dr. Pellman said that he has studied players who had multiple concussions and that "they had all returned to normal. Does that mean there may or may not be problems 10 to 15 years from now? I don't know, but the early objective data say no.' Dr. Pellman says the NFL hasn't studied former players' health because they are no longer employees and are geographically scattered." (Ellen E. Schultz, "A Hobbled Star Battles the NFL," p. A2.)

²⁶⁴ Elliot J. Pellman, et al., "Concussion in Professional Football: Neuropsychological Testing — Part 6," see comments by Julian E. Bailes, p. 1304.

²⁶⁵ Ibid., see comments by Daniel F. Kelly, p. 1304.

²⁶⁶ Ibid., see comments by Joseph Bleiberg, p. 1304.

²⁶⁷ Ibid., see comments by Joseph C. Maroon, p. 1305.

Given the methods and statistical design used, it is difficult to understand how they can comment that 'The strong correlation between the results of clinical and neuropsychological evaluations also provides supportive evidence for the position that there is no evidence in this study of widespread permanent or cumulative effects of single or multiple MTBIs in professional football players.' They only studied the acute neuropsychological effects of single and repeat concussion, and the data presented tell us nothing about potential 'permanent' or long-term complications. The authors cannot assume that there could not be chronic effects, especially since they have only looked at a brief window of time.²⁶⁸

A study carried out by physicians who are not affiliated with the NFL and led by the research director of the Center for the Study of Retired Athletes (CSRA), Kevin M. Guskiewicz, focused specifically on the long-term effects of concussions in former NFL players. As the following excerpt shows, Gukiewicz, et al., reached a different conclusion than did Pellman, et al., regarding possible long-term consequences of MTBIs.

These data describe a significant association between recurrent concussion and MCI, as well as with self-reported memory impairments confirmed by a spouse or close relative. Retired professional football players with three or more concussions were twice as likely to be diagnosed with MCI as those with one or two previous concussions, and five times more likely than those with no previous concussions. This trend continued with respect to self-reported significant memory problems. These findings suggest that the clinical features of dementia-related syndromes ... may be initiated by repetitive cerebral concussions. ²⁶⁹

Another result of the survey conducted by Guskiewicz, et al., involved the prevalence of concussions among retired NFL players. Among former players who participated in the study, 60.8% reported having had at least one concussion during their NFL careers, and 24% reported sustaining three or more concussions.²⁷⁰

Peer reviewers' comments on Guskiewicz, et al., noted, among other points, that relying on self-reported information might affect the accuracy of the data collected. Several peer reviewers also commented on the value and possible implications of the study.

Like all retrospective studies that rely upon self-reported medical histories and health problems, this one is subject to bias in the accuracy with which problems were recalled and reported. Nevertheless, these results are of considerable interest. The authors make appropriate recommendations for further prospective studies...²⁷¹

²⁶⁸ Ibid., see comments by Kevin M. Guskiewicz, p. 1305.

²⁶⁹ Kevin M. Guskiewicz, et al., "Association Between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players," *Neurosurgery*, vol. 57, no. 4, Oct. 2005, p. 723.

²⁷⁰ Ibid., p. 721.

²⁷¹ Ibid., see comments by Alex B. Valadka, p. 725.

Studies such as this have the potential to provide important information [regarding the possibility of neurologic impairment surfacing after a player has retired]. Unfortunately, this particular study is confounded by a critical design flaw of relying on retired athletes to accurately recall events from decades earlier and relating those events to their current memory problems.²⁷²

This study has important and far-reaching implications. To my knowledge, this is one of few studies to show a positive association between repetitive concussion and long-term cognitive impairment and Alzheimer's disease.²⁷³

This is an interesting paper that poses an intriguing hypothesis regarding the consequences of recurrent concussion, not only to create short-term problems, but also to accelerate the decline of cognitive function in later years. While tantalizing, the findings are soft. The data are derived from a questionnaire administered to a group that may have substantial bias, especially considering the recent reports and concerns expressed by physicians and the media.²⁷⁴

This is an extremely valuable contribution. Most concussion studies focus on the days and weeks following the injury with the implicit assumption that recovery to preinjury levels is the end of the issue. The present paper provides strong suggestion that some residua of a concussion may not become manifest until decades after the injury.... The authors are to be commended for clearly stating the limitations of their retrospective self-report experimental design. However, the "gold-standard" methodology would require a multi-decade prospective study.²⁷⁵

This is an important paper on the relationship between cerebral concussion and subsequent cognitive impairment in retired professional football players. Its major flaw, as the authors acknowledge, is that the history of previous concussion was based on the players' "retrospective recall of injury events." Nonetheless, their data strongly suggests there is a cumulative deleterious effect of repeated concussion on later cognitive function. ²⁷⁶

The present study does not dispel uncertainties regarding the relationship between repeated concussions and subsequent onset of brain disorders, most importantly Alzheimer's disease.... Society must provide the author with the necessary funds and incentive to do the study correctly based on professionally obtained prospective data.²⁷⁷

A second article by Guskiewicz, et al., examined another possible long-term consequence of concussions, specifically a possible connection between MTBIs and depression in former NFL players. The authors wrote,

²⁷² Ibid., see comments by Donald Marion, p. 725.

²⁷³ Ibid., see comments by M.R. Ross Bullock, p. 725.

²⁷⁴ Ibid., see comments by Arthur L. Day, p. 726.

²⁷⁵ Ibid., see comments by Joseph Bleiberg.

²⁷⁶ Ibid., see comments by Daniel F. Kelly, p. 726.

²⁷⁷ Ibid., see comments by Charles H. Tator, p. 726.

The findings from our study of retired professional football players support the notion that lifetime prevalence of depression and feelings commonly associated with a depressed state increases as a function of previous head injury exposure.... Our observed threefold prevalence ratio for retired players with three or more concussions is daunting, given that depression is typically characterized by sadness, loss of interest in activities, decreased energy, and loss of confidence and self-esteem. These findings call into question how effectively retired professional football players with a history of three or more concussions are able to meet the mental and physical demands of life after playing professional football. Furthermore, our findings suggest that a single concussion does not provide the risk for subsequent depression, and they provide an extension to the findings on the cumulative risk of repeat concussion demonstrated in collegiate football players. In combination, these suggest that football players with three or more concussions are at a threefold risk for sustaining future concussions, with a subsequent threefold risk of being diagnosed with clinical depression compared with those with limited or no prior history.²⁷⁸

Guskiewicz, et al., then explain the impact that depression may have on an individual, noting that "[d]epression can affect one's ability to function in multiple realms, including interpersonal relationships, productivity at work, and self-care. In older adults, depression is associated with significantly higher health care costs and significant risk of functional decline. ²⁷⁹

Additional findings reported by Guskiewicz, et al., in this article suggest that certain players, because of a combination of injuries and circumstances, may experience a range of problems during retirement. The following excerpt describes these circumstances and problems:

Our findings also suggest that, in general, retired professional football players who have a history of concussion and depressive episodes report greater physical limitations that interfere with their ability to perform daily physical activities compared with those without depression. The SF-36 [Short Form 36] results for mental and physical functioning reveal that those with a history of depression are more likely to be restricted by muscle and joint pain, feel helpless, have difficulty sleeping, and, in general feel as though their health is declining.²⁸⁰ Individuals with a history of depression also reported more alcohol-related problems and were more likely to be separated or divorced."²⁸¹

The journal in which this article appeared did not publish any peer review comments on this article.

²⁷⁸ Kevin M. Guskiewicz, et al., "Recurrent Concussion and Risk of Depression in Retired Professional Football Players," *Medicine and Science in Sports and Exercise*, June 2007, p. 906.

²⁷⁹ Ibid., pp. 907-908.

²⁸⁰ The title of the SF-36 is "Short Form 36 Measurement Model for Functional Assessment of Health and Well-Being," and it "assesses health status and estimates how well a retired athlete functions with activities of daily living." (Kevin M. Guskiewicz, et al., "Recurrent Concussion and Risk of Depression in Retired Professional Football Players," p. 904.)

²⁸¹ Ibid., p. 906.

Susceptibility to an Additional MTBI. A study of 2,905 football players, which was also led by Kevin Guskiewicz, explored the possibility that a player who has suffered one or more concussions is more likely to sustain an additional concussion than an individual who has not had any concussions. In a published article, Guskiewicz, et al., reported that a player who has sustained a concussion, and, in particular, a player who has sustained three or more concussions, has a greater probability of having another concussion than a player who has not had three concussions. The authors wrote,

Players reporting a history of 3 or more previous concussions were 3.0 ... times more likely to have an incident concussion than players with no concussion history.... Our study suggests that players with a history of previous concussions are more likely to have future concussive injuries than those with no history; 1 in 15 players with a concussion may have additional concussions in the same playing season; and previous concussions may be associated with slower recovery of neurological function.... These results illustrate that a history of previous concussions may be associated with an increased risk of future concussive injuries and that these previous concussion may be associated with slower recovery of neurological function following subsequent concussions. Within a given season, there may be a 7- to 10-day window of increased susceptibility for recurrent concussive injury, but this finding should be further studied in a larger sample of athletes with recurrent in-season concussions.

This article was not published in *Neurosurgery*; hence, there are no comments by peer reviewers.

In an article on return-to-play considerations, which are used to determine when it is acceptable, from a medical perspective, for a player who has sustained a concussion to return to practice or to a game, Pellman, et al., suggest that a player who has sustained an MTBI does not have a greater risk of sustaining another concussion than a player who has no history of concussions.

Players who are concussed and return to the same game have fewer initial signs and symptoms than those removed from play. Return to play does not involve a significant risk of a second injury either in the same game or during the season. The current decision-making of NFL team physicians seems appropriate for return to the game after a concussion, when the player has become asymptomatic and does not have memory or cognitive problems.²⁸³

The NFL experience thus suggests that players who become asymptomatic with normal examinations at any time after injury, while the game is still in progress, have been and can continue to be safely returned to play on that day. This indicates that the '15-minutes rule' in the current guidelines may be too conservative for the NFL. Many of the currently accepted guidelines also indicate that any player who experiences loss of consciousness with MTBI

²⁸² Kevin M. Guskiewicz, et al., "Cumulative Effects Associated with Recurrent Concussion in Collegiate Football Players," *Journal of the American Medical Association*, vol. 290, no. 19, Nov. 19, 2003, pp. 2549 and 2554.

²⁸³ Elliot J. Pellman, et al., "Concussion in Professional Football: Players Returning to the Same Game — Part 7," *Neurosurgery*, vol. 56, no. 1, Jan. 2005, p. 79.

should not be allowed to return to play that day.... Although the numbers were small, there were a few players in this study who had recorded loss of consciousness as a result of MTBI and later returned to play in the same game. There was no evidence of any adverse effect of this action. These data suggest that these players were at no increased risk of repeat MTBI or prolonged postconcussion syndrome compared with other players.²⁸⁴

The peer reviewers' comments on Pellman, et al., are as follows:

A study of this magnitude has some inherent limitations, as the authors acknowledge. However, this is an interesting analysis that demonstrates that, at least in the acute phase and during their active playing years, these athletes seem to perform well with a risk for intracranial hemorrhage or a later high incidence of recurrent concussion or postconcussion symptoms.²⁸⁵

The conclusions cited in this article are supported by the data presented.... Multiple studies in the past several years have indicated that the incidence of concussion cited by the athlete questioned after the season is over is many times higher, four to seven times, than that currently reported by the team medical personnel. That most athletes do play through most minor concussions is supported by these studies.²⁸⁶

The present study evaluated the safety of returning concussed professional football players to the same game immediately or after a period of rest.... As would be predicted, players who returned to the same game have significantly lower incidences of cognitive and memory problems than players removed from play or hospitalized This article essentially confirms that the practice by team physicians and trainers in the NFL of not allowing symptomatic or neurologically abnormal athletes to return to play in the same game is a safe practice.²⁸⁷

Return-to-play decisions regarding athletes who sustain concussion can be difficult for the sports medicine team. Pellman et al., in Part 7, describe signs, symptoms, and management of NFL players who sustained concussions and returned to the same game during the 6-year period. The authors of this study conclude that the results of this NFL study differ from previous articles and did not reveal the same return-to-play concerns.²⁸⁸

Chronic Traumatic Encephalopathy (CTE). Chronic traumatic encephalopathy which is also known as dementia pugilistica and is a long-term problem associated with traumatic brain injury, "primarily affects career boxers. The most common symptoms of the condition are dementia and parksonism [apparently, a reference to Parkinson's Disease] caused by repetitive blows to the head over a long

²⁸⁴ Ibid., p. 88.

²⁸⁵ Ibid., see comments by Julian E. Bailes, p. 90.

²⁸⁶ Ibid., see comments by Robert C. Cantu, p. 91.

²⁸⁷ Ibid., see comments by Joseph C. Maroon, p. 91.

²⁸⁸ Ibid., see comments by Russ Romano, p. 91.

period of time. Symptoms begin anywhere between 6 and 40 years after the start of a boxing career, with an average onset of about 16 years."²⁸⁹

In 2002, Dr. Bennet I. Omalu, a neuropathologist and a forensic pathologist with the Office of the Medical Examiner, Allegheny County, PA, performed the autopsy of Mike Webster, a former player for the Pittsburgh Steelers, and found signs of CTE in Webster's brain. Writing in an article that was published in *Neurosurgery* in July 2005, Omalu, et al. described what was found during the autopsy and suggested that additional research was warranted:

... the results of the autopsy of a retired professional football player ... revealed neuropathological changes consistent with long-term repetitive concussive brain injury.²⁹¹ This case draws attention to the need for further studies in the cohort of retired National Football League players to elucidate the neuropathological sequelae of repeated mild traumatic brain injury in professional football.... Autopsy confirmed the presence of coronary atherosclerotic disease with dilated cardiomyopathy.... Chronic traumatic encephalopathy was evident.... This case highlights potential long-term neurodegenerative outcomes in retired professional

²⁸⁹ National Institutes of Health, National Institute of Neurological Disorders and Stroke, "Traumatic Brain Injury: Hope Through Research," available at [http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm].

²⁹⁰ Dr. Omalu studied the brains of four former NFL players after they died: Terry Long, Justin Strzelczyk, Andre Waters, and Mike Webster. Dr. Omalu "found [the brains of the four players] to have had a condition similar to that generally found only in boxers with dementia or people in their 80s.... a condition evidenced by neurofibrillary tangles in the brain's cortex, which can cause memory loss, depression and eventually Alzheimer's disease-like dementia." (Alan Schwarz, "Lineman, Dead at 36, Shed Light on Brain Injuries," New York Times, Jun 15, 2007, p. C14.) Terry Long, a former lineman for the Pittsburgh Steelers, committed suicide, in Jan. 2006, at age 45 ("Ex-Steeler Long Drank Antifreeze to Commit Suicide," Espn.com, Jan. 26, 2006, available at [http://sports.espn.go.com/espn/print?id=2307003&type=story].) Justin Strzelczyk, who also had played for the Steelers, as an offensive lineman, was killed, at age 36, in a car crash. (Schwarz, "Lineman, Dead at 36, Shed Light on Brain Injuries," p. C18.) Following his retirement from the NFL, Strzelczyk "spiraled downward ... enduring a divorce and dabbling with steroid-like substance, and soon before his death complained of depression and hearing voices from what he called 'the evil ones.' He was experiencing an apparent breakdown the morning of Sept. 30, 2004, when, during a 40-mile high-speed police chase in central New York, his pickup truck collided with a tractor-trailer and exploded, killing him instantly." (Ibid.) Andre Waters, a former defensive back for the Philadelphia Eagles, committed suicide at age 44 in Nov. 2006. (Ibid.) Mike Webster died at age 50, in Sept. 2002, of heart failure. (Greg Garber, "A Tormented Soul," Espn.com, Jan. 24, 2005, available at [http://sports.espn.go.com/nfl/news/story?id=1972285].)

Although a diagnosis of CTE is complicated, the following rudimentary description of the process and effect may be useful: "When slides were made of the [brain] matter [from Mike Webster], then magnified 200 times, the telltale red flecks of abnormal protein appeared. The proteins appear when the brain is hit, [Dr. Bennet] Omalu said, but disappear as the healthy brain cells devour them, leading to recovery. Yet when the brain suffers too many blows, the brain cells can't keep up with the protein and eventually give up and die, leaving just the red flecks." (Les Carpenter, "Brain Chaser' Tackles Effects of NFL Hits," Washington Post, Apr. 25, 2007, p. E4.)

National Football League players subjected to repeated mild traumatic brain injury. The prevalence and pathoetiological mechanisms of these possible adverse long-term outcomes and their relation to duration of years of playing football have not been sufficiently studied. We recommend comprehensive clinical and forensic approaches to understand and further elucidate this emergent professional sports hazard.²⁹²

Although Omalu, et al., indicate that CTE was evident in Webster's brain, they also note that further studies are needed. It appears that this was the first article to examine the possibility that professional football players could sustain damage sufficient to cause CTE.

In response to this article, several members of the MTBI Committee submitted a letter in May 2006 to *Neurosurgery* critiquing Omalu, et al., and suggesting that their article should be retracted or revised. An excerpt from Casson, et al., follows:

[We] disagree with the assertion that Omalu et al.'s ... recent article actually reports a case of 'chronic traumatic encephalopathy in a National Football League (NFL) player.' We base our opinion on two serious flaws in Omalu et al.'s article, namely a serious misinterpretation of their neuropathological findings in relation to the tetrad characteristics of chronic traumatic encephalopathy and a failure to provide an adequate clinical history.... We have demonstrated that Omalu et al.'s ... case does not meet the clinical or neuropathological criteria of chronic traumatic encephalopathy. We, therefore, urge the authors to retract their paper or sufficiently revise it and its title after more detailed investigation of this case.²⁹³

Omalu, et al., replied to the Casson, et al., letter and others in the field of neurology also commented on the article and the Casson et al. letter. In their reply, Omalu, et al., explained why they would not withdraw their article and concluded by encouraging the NFL to study the long-term consequences of MTBI. In concluding their letter, Omalu, et al., wrote,

In fact, our case is important primarily because it indicates that there may be brain damage in NFL players that is currently under-reported, because of a lack of long-term clinical follow-up focused on evaluating such a condition. We suggest that the NFL begin examining the long-term effects of brain injury in its former players. We would be happy to collaborate with the Mild Traumatic Brain Injury Committee and the NFL in developing and implementing an optimal research program that will address these newly emerging issues.²⁹⁴

²⁹² Bennet I. Omalu, et al., "Chronic Traumatic Encephalopathy in a National Football League Player," *Neurosurgery*, vol. 57, no. 1, July 2005, p. 128.

²⁹³ Ira R. Casson, Elliot J. Pellman, and David C. Viano, "Chronic Traumatic Encephalopathy in a National Football League Player," correspondence, *Neurosurgery*, vol. 58, no. 5, May 2006, p. E1003.

²⁹⁴ Bennet I. Omalu, et al., "Chronic Traumatic Encephalopathy in a National Football League Player," correspondence, *Neurosurgery*, vol. 58, no. 5, May 2006, p. E1003.

The following excerpts from others' letters are provided to show the range of comments offered by others who addressed Omalu, et al.'s, July 2005 article and Casson, et al.'s, May 2006 correspondence. Although one correspondent supported retraction of the Omalu, et al., article; others note the article's limitations but suggest that it has value.

... I agree that retraction or a major revision by the authors is warranted. 295

They [Casson, et al.] do not dispute his [Omalu, et al.] findings, they simply dispute the name Omalu et al. have given to those findings.... In summary, I see the Casson et al. letter as raising several valid points regarding the intrinsic limitations of the case material used in Omalu et al.'s study. However, because these limitations were noted by Omalu et al. in the published version, I do not see the point of publishing a letter reiterating them.²⁹⁶

[Casson, et al.,] should be thanked for compiling this detailed historical review of our understanding of the neuropathology of chronic brain injury.... Omalu et al.'s report may serve to stimulate interest in the area of neurodegenerative histological findings in athletes. However, the bar has clearly been raised. Future studies will need to use standardized or widely accepted histological criteria in addition to firm and accurate medical histories.²⁹⁷

Casson et al., conveniently omitted the obvious contribution of this [Omalu, et al.] study. Namely, this is a seminal study in the field.... Casson et al.'s letter seems to have exceeded protocol for scientifically providing an additional opinion for a published story. Specifically, they took an extreme stand in actually urging the authors to retract the article.... Articles should be considered for retraction if they contain fabricated data, contamination of data, or allegation of misconduct. It is my opinion that there is no justification for retracting this article.²⁹⁸

As members of the Mild Traumatic Brain Injury Committee of the NFL, and clinician-scientists that are clearly devoted to the investigation of sports-related concussion, Drs. Casson, Pellman, and Viano should welcome the contribution from Omalu et al. and consider the findings of that report highly relevant to their own research, rather than recommending retraction of the article. The need to obtain more details regarding premorbid neuropsychological deficits and specific episodes of concussion is clearly recognized and stated by Omalu et al. ... in their

²⁹⁵ Daniel F. Kelly, "Chronic Traumatic Encephalopathy in a National Football League Player," correspondence, *Neurosurgery*, vol. 58, no. 5, May 2006, p. E1003.

²⁹⁶ Joseph Bleiberg, "Chronic Traumatic Encephalopathy in a National Football League Player," correspondence, *Neurosurgery*, vol. 58, no. 5, May 2006, p. E1003.

²⁹⁷ Alex B. Valadka, "Chronic Traumatic Encephalopathy in a National Football League Player," correspondence, *Neurosurgery*, vol. 58, no. 5, May 2006, p. E1003.

²⁹⁸ Kenneth C. Kutner, "Chronic Traumatic Encephalopathy in a National Football League Player," correspondence, *Neurosurgery*, vol. 58, no. 5, May 2006, p. E1003.

paper, but the histopathological findings are clearly described and consistent with a previous history of brain injury.²⁹⁹

In November 2006, Omalu, et al., presented the results of an examination of the brain of another retired NFL player. The autopsy confirmed that this individual had CTE, but it also discovered "neuropathological features that differ from those of the first reported case." The reasons for the differences were not clear, and, again, Omalu called for further studies "to identify and define the neuropathological cascades of chronic traumatic encephalopathy in football players, which may form the basis for prophylaxis and therapeutics." Excerpts from peer reviewers' comments are as follow:

This is an interesting study linking the chronic head trauma in professional football players with chronic traumatic encephalopathy. There is a temporal association of the symptoms with the patient's football career. Also, it does not prove that head injury from playing football was the sole cause of this patient's disease; the association is intriguing and is important to report.³⁰²

With such multifactorial and incomplete history, I think it is extremely speculative to suggest that his [former player] psychosocial behavior and neuropathological findings are attributable to football-induced traumatic encephalopathy, especially because he demonstrated no residual evidence of a post concussion syndrome after his one documented cerebral concussion, after which he returned to full football participation for several years. Nevertheless, although more than daunting, to perform postmortem neuropathological examinations on all NFL Hall of Fame inductees would be of interest. 303

Following on their initial case report, this autopsy study is of interest and further raises the question of the possibility of chronic or cumulative effects of multiple, subclinical concussions resulting in neurodegenerative changes.... Notwithstanding the absence of documentation of multiple clinical concussive episodes, this case nonetheless stimulates the discussion of whether or not, in a small number of players, such football exposure can cause a widespread neurodegenerative process with ultimate clinical manifestations.³⁰⁴

This article adds to the increasing literature regarding cognitive deficits associated with low-grade repetitive head injury. Although, as a case report, no

²⁹⁹ Donald W. Marion, "Chronic Traumatic Encephalopathy in a National Football League Player," correspondence, *Neurosurgery*, vol. 58, no. 5, May 2006, p. E1003.

³⁰⁰ Bennet I. Omalu, et al., "Chronic Traumatic Encephalopathy in a National Football League Player: Part II," *Neurosurgery*, vol. 59, no. 5, Nov. 2006, p. 1086.

³⁰¹ Ibid.

³⁰² Ibid., see comments by Kenneth Aldape, p. 1092.

³⁰³ Ibid., see comments by Joseph C. Maroon, p. 1092.

³⁰⁴ Ibid., see comments by Julian E. Bailes, p. 1093.

definitive statements can be made, it is important to have such cases presented and discussed.³⁰⁵

The authors compare and contrast this case with a previous case report. The relationship of the onset of his depressive disorder after his history of participation in football is purely temporal. This is a difficult relationship, given a potential history of antisocial behavior before his retirement. It becomes additionally more complex given a history of steroid use.³⁰⁶

In the August 2007 issue of *Neurosurgery*, Robert C. Cantu offered his comments on the CTE issue.³⁰⁷ Excerpts from his comments follow:

The NFL's own publications in this journal [Neurosurgery] on concussions state that they had seen no cases of CTE in the NFL.... That finding is not a surprise as the NFL study included only active players in their 20s and 30s during a short 6-year window from 1996 to 2001.

It was Corsellis who also reported CTE not only in boxers but other sports with a high risk of head injury, including those in which head injury occurred in declining frequency; among these were jockeys (especially steeplechasers), professional wrestlers, parachutists, and even a case of battered wife syndrome. With this history, it is no surprise to have cases from NFL football.³⁰⁸

³⁰⁵ Ibid., see comments by Colin Smith, p. 1093.

³⁰⁶ Ibid., see comments by Min Park, Andy Nguyen, and Michael L. Levy, p. 1093.

³⁰⁷ A critique by Cantu of the NFL's research on MTBI might provide some insight into why other, though not all, professionals in the field of neurology raise questions about the articles published by the MTBI Committee. Cantu wrote: "Other significant limitations of the NFL studies include the following: 1) History of concussion: previous concussions either in the NFL in the years before the study began or during their playing careers in high school, college, or other levels of football were not included. 2) The population of NFL players changes from year to year: new players enter the league, older players leave the league, and we do not know the number of players who constituted the 1996 population who are still in the league in subsequent years. 3) There was difficulty collecting data on loss of consciousness; the initial data collection sheet did not ask for data regarding loss of consciousness. 4) This was a multisite study with numerous different examiners; there was no uniform method of evaluation of concussion in this study. 5) Return to play data were collected on players with initial and repeat concussions: there are many other factors that go into the decision of whether or not the player should return to play, including the importance of the player to the team; the importance of the upcoming game to the team; and pressure from owners, players, and their families, coaches, agents, and media may certainly influence the final decision on when the player returns to play. 6) The results apply to mainly NFL-level players: extrapolation to younger players has not been demonstrated." (Robert C. Cantu, "Chronic Traumatic Encephalopathy in the National Football League," Neurosurgery, vol. 61, no. 2, Aug. 2007, pp. 223-224.) Also see text at footnote 329.

³⁰⁸ Ibid., p. 224. "Corsellis" in this quotation refers to one or both of these articles: J.A. Corsellis, C.J. Bruton CJ, and D. Freeman-Browne, "The Aftermath of Boxing," *Psychological Medicine*, vol 3, 1973, pp. 270-303; and J.A. Corsellis, "Brain Damage in Sport," *Lancet*, 1, 1976, pp. 401-402.

... I have personally examined and spoken with a number of retired NFL players with postconcussion/CTE symptoms. Only an immediate prospective study will determine the true incidence of this problem. Although this study could be funded by the NFL charities, the NFL should refrain from introducing potential bias with regard to the team of neurosurgeons, neurologists, neuropsychiatrists, and neuropathologists with athletic head injury expertise chosen to carry out the study.³⁰⁹

Finally, it is clear that not all players with long concussion histories have met premature and horrific ends to their lives. However, as the list of NFL players retired as a result of post-concussion symptoms (e.g., Harry Carson, Al Toon, Merril Hoge, Troy Aikman, Steve Young, Ted Johnson, Wayne Chrebet) grows and as the number of documented CTE cases increases, I believe the time for independent study of the problem as well as NFL recognition that there is a problem is now.³¹⁰

NFL's Approach to MTBI. It is unclear whether the NFL has, or has had, a league-wide policy on MTBI that teams — including medical staff, coaches, and players — are required to follow. A news article from fall 2006 stated: "The NFL allows each team to manage concussions as it sees fit. When a player is injured, the team doctor, sometimes with input from trainers and specialists, decides when he can return to the field." In 2007, following league meetings in March and May, the NFL undertook several initiatives involving the management of MTBI, which are as follow: 312

- Held a medical and scientific conference (known popularly as the "concussion summit") on concussions in June. Physicians and head trainers from every team, and active players and NFLPA medical representatives attended. Doctors and scientists from the NFL and from outside the league gave presentations.
- Prepared a pamphlet for players and their families that, among other things, describes the symptoms of a concussion.
- Established a hotline to be used for reporting confidentially when a player is being forced to practice or play despite medical advice that says he should not play.
- Worked with the NFLPA's medical advisors, prepared a summary of key factors to be used by team doctors and athletic trainers in

³⁰⁹ Ibid.

³¹⁰ Ibid.

³¹¹ Keating, "Doctor Yes."

³¹² "Goodell Orders Teams to Concussion Meeting," *NFL News*, May 2, 2007, available at [http://www.nfl.com/news/story/10162742]; Letter from Roger Goodell, Commissioner, National Football League, to Chief Executives, Club Presidents, General Managers, Head Coaches, Team Physicians, and Head Athletic Trainers, "Materials re Management of Concussions," memorandum, Aug. 10, 2007, p. 1.

determining when it is safe for a player to practice, or to return to the same game in which the concussion occurred.

- Expanded the use of neuropsychological testing so that, before the beginning of the 2007 season, all NFL players underwent testing.
- Directed that players removed from a game due to a concussion be re-tested.
- Continued to enforce safety rules involving the use and proper wearing of helmets. And,
- Continued to research concussions with "a particular focus on longterm effects" and expanded the membership of its MTBI Committee.³¹³

The concussion summit included presentations by members of the MTBI Committee and presentations by at least two neurologists who either have written articles that conflict with articles published by MTBI Committee members or have critiqued the committee's research.

The establishment of a hotline has the potential to aid a player who is pressured to play after sustaining a concussion or who observes that a teammate is being pressured to play. It is appropriate to expect a player to take responsibility for his health, and team personnel may use the hotline, too. However, considering the financial incentives (as discussed above) that might convince someone to play with a concussion, some may inquire why owners, coaches, medical staff, and other team personnel are not prohibited from implicitly or explicitly pressuring a player to practice, or to play in a game, when it is not medically advisable to do so. As quoted in a news article, a former tight end for the New Orleans Saints, Ernie Conwell, addresses this problem and offers a cautionary note that "stiffer guidelines" might have an unintended effect:

There's already kind of a counterculture in the N.F.L. of self-treating, of not letting trainers and doctors know when something's wrong with you My biggest concern [about stiffer guidelines on how to deal with players who may have suffered concussions] is that we'll push players away Guys will say 'Hey man, be careful, you don't want to say anything about getting dinged because they might rip you out of the game, or you might be labeled as a guy with a soft head.³¹⁴

³¹³ Letter from Roger Goodell, Commissioner, National Football League, and Eugene Upshaw, Executive Director, NFL Players Association, to NFL players, Aug. 2007, pp. 1-2; National Football League, "NFL Outlines for Players Steps Taken to Address Concussions," news release, Aug. 14, 2007, pp. 1-2.

³¹⁴ Alan Schwarz, "Player Silence on Concussions May Block N.F.L. Guidelines," *New York Times*, June 20, 2007, available at [http://www.nytimes.com/2007/06/20/sports/football/20concussions.html].

The case of former New York Jets wide receiver Wayne Chrebet, as reported by the *New York Times*, shows how he viewed the decision to play, after having had six concussions diagnosed during his 11-year NFL career.

"If they took it [the decision to play] out of my hands, there was nothing I could do about it," Chrebet said. "I'd have to do what they said." On the other hand, if he were not permitted to come back, there might not have been a Wayne Chrebet with the Jets. He was an undersized receiver from Hofstra, an obscure college by N.F.L. standards, who felt he did not have the luxury to miss a game. "Especially players who were in my situation, you can't afford to take a play off," he said. Chrebet cited the story of Wally Pipp, who was replaced in the Yankees' starting lineup by Lou Gehrig and never regained his spot. In the N.F.L., nonguaranteed contracts add to the normal competitiveness and insecurity. "You take one play off, and somebody takes your spot," Chrebet said. "They make a play, [and] it [your career] could be over. 315

The last item in the list of NFL initiatives above mentions additional MTBI research that is planned or ongoing; a list of these studies is in **Appendix B**. Additionally, NFL Charities has awarded, during 2003-2007, grants for research involving, among other things, concussions, MTBI, and related topics. **Table 17** includes a list of these grants.

Table 17. Recipients of NFL Charities Grants for MTBI and Related Research, 2003-2007

Institution	Amounts and Years of Grants ^b	Description of Research or Title of Study
Biokinetics and Associates, Ltd. ^a	— \$189,914 2005	— "MTBI Advanced Concussion Research Study"
	— \$175,900 2006	— "Concussion studies"
	— \$105,000 2006	— "MTBI Advanced Concussion Research Study"
	— \$111,413 2007	— "MTBI Advanced Concussion Research Study"
Institute for Injury Research ^c	— \$155,000 2005	— "Concussion-Comparing Injuries in the NFL Animal Model with those from an Established Head Injury Model by Marmarou."
	— \$75,000 2007	— "Concussions-Studying Protein Deposits in the Brain After Concussions"
Mark R. Lovell	— \$7,500 2007	"NFL Pilot Study Neuropsychological Testing"

³¹⁵ Rhoden, "A Jet Who Led With His Head, and His Heart."

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Institution	Amounts and Years of Grants ^b	Description of Research or Title of Study
University of Maryland- Baltimore	— \$59,000 2003	"Assessment of brain blood flow following concussion."
Wayne State University Sports Lab ^d	- \$200,000 2003	— "Concussion studies"
	— \$180,000 2004	— "Concussion studies"
	— \$45,000 2005	— "Mouth guards-Development of a Mandible and Teeth for the Hybrid III Dummy Head to Test the Influence of Mouth guards on Risk of Concussions"
	\$170,000 2006	— "Helmet and Mouth Guard- Concussion Studies"
	— \$25,000 2007	— "Mouth guard and Helmet Testing"
	— \$352,887 2007	— "Helmet Impact Study"

Source: Letter from Roger Goodell, Commissioner, National Football League, to Reps. John Conyers, Jr., and Lamar S. Smith, Nov. 2, 2007, attachment 8.

- a. Biokinetics and Associates, Ltd., is a Canadian firm that, according to its mission statement, "provides engineered solutions to human impact protection for sports, transportation and defence/law enforcement applications." (Biokinetics, "Mission," available at [http://www.biokinetics.com/profile_index.html].)
- b. Amounts have been rounded to the nearest dollar.
- c. David Viano, who is co-chair of the MTBI Committee, is the president of the Institute for Injury Prevention. (David C. Viano, "Résumé," provided by the House Committee on the Judiciary to the author on Nov. 6, 2007, p. 5.)
- d. Apparently, the full name of this organization is Sports Injury Biomechanics Lab. David Viano, who is co-chair of the MTBI Committee, is the director of the Sports Injury Biomechanics Lab. (Wayne State University, "Sports Injury Biomechanics Lab," available at [http://ttb.eng.wayne.edu/]; Viano, "Résumé," p. 1.)

As reported by *ESPN.com*, the NFL has taken, or plans to take, some additional steps regarding its MTBI Committee. Reportedly, the commissioner has told the MTBI Committee "to involve new researchers in its work," and a member of the committee said: "We're going to reach out to other people, to all the experts in MTBI, and try to have an open, meaningful scientific dialogue." Thom Mayer, the NFLPA's medical advisor, reportedly said: "We [apparently, this is a reference to the NFLPA] expect to have a seat at the table for virtually anything that occurs from

³¹⁶ Peter Keating, "NFL Retools Approach to Concussion Research," *ESPN.com*, Apr. 20, 2007, available at [http://sports.espn.go.com/nfl/news/story?id=2844041].

this point forward."³¹⁷ Additionally, the MTBI committee reportedly has subjected its research findings "to a new round of statistical analysis...." and has asked team doctors and consultants to provide "hundreds of neuropsychological tests conducted on NFL players" that apparently had not been included in studies on the effects of concussions.³¹⁸

The "NFL Player Concussion Pamphlet" identifies and describes the most common symptoms of concussions and also addresses, in question and answer format, a number of concussion-related subjects. Two of these questions and the NFL's responses are as follow:

Am I at risk for further injury if I have had a concussion? Current research with professional athletes has shown that you should not be at greater risk of further injury once you receive proper medical care for a concussion and are free of symptoms.

If I have had more than one concussion, am I at increased risk for another injury? Current research with profession athletes has not shown that having more than one or two concussions leads to permanent problems if each injury is managed properly. It is important to understand that there is no magic number for how many concussions is too many. Research is currently underway to determine if there are any long-term effects of concussion in NFL athletes.³¹⁹

These responses apparently rely exclusively on the MTBI Committee's studies, for no mention is made of other research that addresses the possible long-term consequences of sustaining one or more concussions (this research is presented above). The following comments by researcher Kevin Guskiewicz and Greg Aiello, senior vice president of media relations for the NFL, as reported in the *New York Times*, capture the different perspectives:

[Kevin Guskiewicz] noted that "The first half of their statement is false.... And the second part, if they're managed properly? What does that mean? They're just trying to raise ambiguity when the science is becoming more and more clear." Greg Aiello, NFL spokesman, responded in a statement: "We certainly respect the work that Dr. Guskiewicz and others have done on this subject and look forward to continuing to work with him. Our medical advisers, including neurosurgeons and neurologists, do not fully share his view of the science. We are conducting research on long-term effects of concussions that we hope will clarify this important issue." 320

³¹⁷ Ibid.

³¹⁸ Ibid.

³¹⁹ National Football League, "NFL Player Concussion Pamphlet," n.d. (Considering the context in which a reproduction of pamphlet material was received, the pamphlet most likely was produced in 2007.)

³²⁰ Schwarz, "For Jets, Silence on Concussions Signals Unease," p. A20.

Another development in 2007 was that the MTBI Committee reaffirmed the following summary of return-to-play considerations for players who sustain concussions:

Team physicians and athletic trainers should continue to exercise their clinical judgment and expertise in the treatment of each player who sustains a concussion and to avail themselves of additional expert consultation when clinically indicated. We encourage team physicians and athletic trainers to continue to take a conservative approach to treating concussion.

Team physicians and athletic trainers should continue to take the time to obtain a thorough history, including inquiring specifically about the common symptoms of concussion, and to conduct a thorough neurological examination, including mental status testing at rest and post-exertional testing, before making return to play decisions in a game or practice.

The essential criteria for consideration of return to play remain unchanged. The player should be completely asymptomatic and have a normal neurologic examination, including mental status testing at rest and post-exertional testing, before being considered for return to play.

Team physicians and athletic trainers should continue to take into account certain symptoms and signs that have been associated with a delayed recovery when making return to play decisions. These include confusion, problems with immediate recall, disorientation to time, place and person, anterograde and retrograde amnesia, fatigue, blurred vision and presence of three or more signs and symptoms of concussion.

If the team medical staff determines a player was unconscious, the player should not be returned to the same game or practice.

Team physicians and athletic trainers should continue to consider the player's history of concussion, including number and time between incidents, type and severity of blow, and time to recover.

Team physicians and athletic trainers should continue to educate players about concussion and to emphasize the need for players to be forthright about physical and neurological complaints associated with concussion.³²¹

The third item from the bottom, which advises that a player who was unconscious should not be returned to the same game or practice, appears to conflict with an article written by members of the MTBI Committee. The relevant portion of the 2005 *Neurosurgery* article is as follows:

Many of the currently accepted guidelines also indicate that any player who experiences loss of consciousness with MTBI should not be allowed to return to play that day Although the numbers were small, there were a few players in this study who had recorded loss of consciousness as a result of MTBI and later returned to play in the same game. There was no evidence of any adverse effect

³²¹ Letter from Roger Goodell, Commissioner, National Football League, and Eugene Upshaw, Executive Director, NFL Players Association, to NFL players, Aug. 2007, p. 5.

of this action. These data suggest that these players were at no increased risk of repeat MTBI or prolonged postconcussion syndrome compared with other players.³²²

Without additional information, the reason for the discrepancy between the league's return-to-play guidelines and the committee's article is unknown. The league's general counsel reportedly stated that the NFL was "erring on the side of player safety ... it may be that a player will be held out of a game when it is not medically required or indicated by the data. Certainly it's a less-risky approach in terms of player safety.... It reflects an effort to avoid this debate going forward."³²³

In the same *Neurosurgery* article, Pellman, et al., also discuss various factors that may play a role in deciding when a player may return to the game or practice. They cite the player's medical condition as the most important factor, but then appear to acknowledge that other considerations also may influence the return-to-play decision. Pellman, et al., wrote:

Although the medical condition of the player certainly is the most important factor in determining return-to-play decisions by team physicians, there are many other factors that go into the decision of when the player should return to play. The importance of the player to the team; the importance of the game to the team; and pressure from owners, players and their families, coaches, agents, and media certainly may influence the decision of when the player returns to play. The authors believe, however, that the medical factors regarding the patient's recovery are and should be the overriding factors that guide the team physicians' decisions-making on return to play. 324

Funding for the Retirement Plan

Maintaining full funds for the retirement plan is a priority of the NFL and the NFLPA, and is made possible by the use of actuarial assumptions (or factors) and methods, and by ensuring that benefits are awarded only to eligible individuals. Under the CBA, the amount of money needed to fund certain benefits, including the retirement plan, is determined using "negotiated actuarial factors." The factors (or assumptions) are "determined by collective bargaining" and are "acceptable to the plan's Enrolled Actuary." At a congressional hearing in 2007, the plan counsel

³²² Elliot J. Pellman, et al., "Concussion in Professional Football: Players Returning to the Same Game — Part 7," p. 88.

³²³ Alan Schwarz, "New Advice by N.F.L. in Handling Concussions," *New York Times*, Aug. 21, 2007, available at [http://www.nytimes.com/2007/08/21/sports/football/21concussions.html].

³²⁴ Elliot J. Pellman, et al., "Concussion in Professional Football: Players Returning to the Same Game — Part 7," p. 89.

³²⁵ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 5. In 1993, a single plan counsel, Groom Law Group, and a single plan actuary, Aon Corporation, were selected for the retirement plan. (Ibid.)

NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," (continued...)

stated: "Because of the repeated increases in benefits and thus liabilities, the Retirement Plan is somewhat under funded from an actuarial point of view. Both the Players Association and the NFL view pension funding as a priority, and full funding may occur in the next few years, at least until the next negotiated benefit increase." 327

The use of actuarial assumptions and methods is necessary to ensure that a benefit plan has sufficient funds to meet its obligations — that is, to pay benefits to eligible individuals. Accordingly, it is necessary "that only those persons who qualify for the benefits receive them."³²⁸ According to an article that appeared in the *Washington Post Magazine*, and which quoted the executive director of the NFLPA, Gene Upshaw, the players association is committed to ensuring that funds are available for eligible players. An excerpt from the article follows:

[Gene Upshaw] fears that, if disability payments "go to any borderline cases out there," the floodgates will open, and there "might be thousands" of claims from NFL reitrees who will "say they hurt somewhere on their bodies.... Heck, a lot of guys have little things." He says that the league couldn't endure such a press of claims. "We couldn't afford that," he says. "And the [active] players wouldn't go for it.... The players right now give up \$82,000 a year [on average] to fund all the things we're doing with disability [payments] and pensions.... We can't pay for everything for all the [retirees] asking for it. We want to protect money for the retired players who really need and deserve it."³²⁹

Appendix J of the CBA contains the actuarial assumptions and actuarial cost method used to determine how much money is needed to fund the benefits provided by the retirement plan. Some of the determine how much money is needed to fund the retirement plan. Some of the actuarial assumptions in Appendix J are based on established tables, such as the 1980 Railroad Retirement Board rates, which is used for the "Remarriage and mortality rates for widow's benefit" factor; and *The RP-2000 Table*, which is used for "Mortality rates" and "Disability mortality before age sixty-five." The "Football

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p. 5; Letter from Goodell to Reps. Conyers and Smith, p. 10.

³²⁷ U.S. Congress, House Committee on the Judiciary, Subcommittee on Commercial and Administrative Law, "The National Football League's System for Compensating Retired Players: An Uneven Playing Field?" statement of Douglas W. Ell, Plan Counsel for Bert Bell/Pete Rozelle NFL Player Retirement Plan, unpublished hearing, 110th Cong., 1st sess., June 26, 2007, p. 10.

³²⁸ U.S. Congress, House Committee on the Judiciary, Subcommittee on Commercial and Administrative Law, The National Football League's System for Compensating Retired Players: An Uneven Playing Field?" statement of Dennis Curran, Senior Vice President, National Football League, unpublished hearing, 110th Cong., 1st sess., June 26, 2007, p. 4.

³²⁹ Leahy, "The Pain Game," p. 22.

³³⁰ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 203.

³³¹ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, pp. 282-283. The 1980 Railroad Retirement Board rates are (continued...)

related disability rates" factor apparently is not based on a table. Instead, the disability rates are the following: "As of April 1, 2007, the rates are "[.10%] per year for active players and [.08%] per year for inactive players until age forty-five, after which it becomes zero. Active players are assumed to become inactive after one year or age thirty, whichever comes later." The method and information used for determining these rates is unclear. The NFLPA has noted that "the amount to fund the Retirement Plan is calculated actuarially, in accordance with federal law." Is it possible that retired (that is, inactive) players' needs for medical care exceed the amount of funds for disability benefits that are calculated using this disability rate?

What Is the Extent of the NFLPA's Capacity?

The extent of the NFLPA's authority and capabilities regarding health and safety issues, and its position on such issues are, at times, unclear. For example, the NFL has a number of committees that deal with injuries, safety, and health. Apparently, the NFLPA does not have any similar committees or entities, although, along with the NFL, it is part of the joint committee on player safety and welfare.³³⁴ The NFLPA has a medical advisor; but, apparently, this is not a full-time position, for the current advisor is CEO and president of BestPractices and chairman of the Department of Emergency Medicine, Inova Fairfax Hospital.³³⁵ Additionally, it is unclear what resources, including staff, are available to the medical advisor.

The NFLPA apparently is not included in discussions about proposed rule changes that may affect the health and safety of players. Furthermore, the description of the process for addressing rule changes that might adversely affect player safety shows that, ultimately, neither the joint committee, the players association, nor the

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available at U.S. Railroad Retirement Board, "Financial, Actuarial and Statistical," [http://www.rrb.gov/mep/fin_act_stat.asp]. The other document ,*The RP-2000 Mortality Tables*, is available at [http://www.soa.org/files/pdf/rp00_mortalitytables.pdf].

³³² National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 282.

³³³ Letter from Upshaw to Reps. Convers. Smith. Sanchez. and Cannon. p. 29.

In the absence of evidence of the committee's accomplishments, certain features of the committee suggest that its influence might be limited. The committee holds only two regular meetings per year, although special meetings may be convened, and the committee does not have the power "to commit or bind" the NFLPA or the NFL on any issues. (National Football League and NFL Players Association, *NFL Collective Bargaining Agreement, 2006-2012*, Mar. 8, 2006, p. 38.) The names of the NFLPA's 13 departments are: Benefits Department, Communications Department, Executive Department, Finance and Asset Management Department, Financial Programs and Advisor Administration Department, Information Systems, Legal Department, Membership Services, NFL PLAYERS Department, NFLPA Retired Players Department, Player Development, Regional Directors, and Salary Cap and Agent Administration. (NFL Players Association, "Departments," n.d., available at [http://www.nflplayers.com/user/template.aspx?fmid=181&l mid=238&pid=0&type=1].)

³³⁵ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 11.

arbitrator (if one is involved) has authority to modify or rescind a potentially problematic proposed rule change. (The issue of rule changes is discussed above.)

The subject of MTBI research and guidelines, in particular, raises several questions regarding whether the players association has sufficient capacity and authority to participate effectively in matters involving safety and health issues. For example, while members of the MTBI Committee have been involved in an ongoing dialogue with other professionals in the field of neurology (as documented above), it appears that the NFLPA has not commented publicly on any of the issues, such as the possible long-term effects of concussions and the possibility that multiple mild traumatic brain injuries could result in CTE. The NFLPA has "supported and/or participated in several studies concerning the physical effects of playing professional football." Those studies include "[s]tudies conducted by the Center for the Study of Retired Professional Athletes at the University of North Carolina at Chapel Hill, including the 'Recurrent Concussion and Risk of Depression in Retired Professional Football Players' study done by Dr. Kevin M. Guskiewicz and others in 2006."

A joint NFL-NFLPA letter on concussions and concussion management noted that the NFLPA's medical advisor had attended the June 2007 "concussion summit" and that he "will remain closely involved" in ongoing projects involving MTBI research. The extent of the authority of the NFLPA medical advisor regarding the committee's decisions, actions, and recommendations is unclear, as are his possible courses of action, if any, should he disagree with the decisions of the committee. Additionally, the NFLPA's involvement in the MTBI's development of the concussion management guidelines and, specifically, the return-to-play guidelines is unclear.

Medical Care for Active Players

Access to Medical Records. Under the CBA, a player may examine his medical records and athletic trainers' records only twice per year: "once during the pre-season and [once] after the regular season." Additionally, he may obtain a copy of the records during the off-season. The rationale for not permitting a player to see his records during the pre-season and regular season is unclear. While obtaining records after the season is useful for the player who wants to, among other

³³⁶ Ibid., p. 12.

³³⁷ Ibid., pp. 12-13.

³³⁸ Letter from Goodell and Upshaw to NFL players, pp. 1-2.

³³⁹ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 199. Having access to one's medical records, albeit only twice per year, apparently is an improvement. As quoted in the *New York Times* in 2002, Gene Upshaw noted the following changes to players' medical care: "Before 1986-87, guys could not select the doctor for their surgery, they could not get second opinions and they could not even see a copy of their medical records.... All of that is in place now." (Thomas George, "Care by Team Doctors Raises Conflict Issue.")

³⁴⁰ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 199.

things, maintain his own medical history, timely access to the records might be useful to a player who has been injured and is receiving, or has received, medical treatment. Furthermore, a player might be more likely to recognize inaccurate, incomplete, or erroneous information if he is permitted to examine his records during the season, rather than having to wait until the conclusion of the season. Team medical staff, however, may not have time during the season to provide access to, or copies of, medical records, because they are fulfilling their primary responsibility, which is to diagnose and treat injured players. The access issue also raises the question of whether a player is permitted to have corrections added to his health records.

In a reminder to players to review their medical records following the season, the NFLPA touched on several issues related to the importance of knowing what is in medical records created and maintained by the team. The NFLPA stated the following:

With injuries being such a critical factor in determining the quality and longevity of an NFL player's career, it is important for players to become knowledgeable about the injuries they sustain and to learn what their club medical staff thinks about those injuries....

According to Tim English, NFLPA Staff Counsel who regularly represents injured NFL players in Injury Grievance arbitrations, "players who review their club's medical records for the first time while preparing their arbitrations are often surprised to read what has been written about their injuries by the club doctors and trainers. The level of detail in the records far exceeds what is told to them by the club." Invariably, those players regret not having taken the time to review their records previously.

Many times, the additional information contained in the club's records may assist a player in planning or altering his off-season treatment and training activity. All too often during the season a player who sustains an injury is only focused on getting back out on the field, and not on the extent of his injury and the best course of action to take for long-term health. The off-season is therefore the time to re-evaluate those injuries, and a review of the club medical and trainers' records is the place to start.³⁴¹

Arrangements for Medical Care and Treatment. Article XLIV of the CBA governs the players' right to medical care and treatment. As the employer, a team provides medical care for its players, which includes team physicians and athletic trainers. Under the CBA, a team's medical staff must include a board-certified orthopedic surgeon; the team is responsible for the cost of medical services that its physicians provide; and all full-time head trainers and assistant trainers must be certified by the National Athletic Trainers Association.³⁴²

³⁴¹ NFL Players Association, "News and Events: Off-Season and Medical Records, Off-Season Is the Time for Players to Review Their Medical Records," available at [http://www.nflpa.org/newsandevents/021908.aspx] as of Feb. 21, 2008, on file with the author.

³⁴² National Football League and NFL Players Association, NFL Collective Bargaining (continued...)

Article XLIV includes several additional safeguards for players, including the following:

If a Club physician advises a coach or other Club representative of a player's physical condition which adversely affects the player's performance or health, the physician will also advise the player. If such condition could be significantly aggravated by continued performance, the physician will advise the player of such fact in writing before the player is again allowed to perform on-field activity.³⁴³

While the requirement to provide written notification to a player is an important safeguard, it is unclear whether this step would be feasible in some situations. For example, is it possible to provide written notification to players during a game?

A player may seek a second opinion, and he may have his team pay for the costs associated with doing so as long as he follows this provision in the CBA:

A player will have the opportunity to obtain a second medical opinion. As a condition of the responsibility of the Club for the costs of medical services rendered by the physician furnishing the second opinion, the player must (a) consult with the Club physician in advance concerning the other physician; and (b) the Club physician must be furnished promptly with a report concerning the diagnosis, examination and course of treatment recommended by the other physician.³⁴⁴

At least one former team doctor has suggested, however, that some players may believe the team prefers that they not seek a second option. As quoted in a news article, Dr. Robert Huizenga, a team doctor for the Oakland Raiders and past president of the National Football League Team Physicians Society, "said he always suspected that the Raiders he treated believed it would be held against them if they sought a second opinion. 'Some of them were afraid to even admit to being injured at all,' Dr. Huizenga said...."

Although it is not known whether any team has discouraged a player from seeking a second opinion, the expense involved and the possibility that a non-team doctor's diagnosis and recommendation for treatment might conflict with, or be more costly than, the team doctor's diagnosis and recommendation might have some bearing on a team's perspective on second opinions. It is unclear whether the team would be required to pay for any non-surgical treatment recommended by a non-team physician. Under the CBA, a team will pay for a player's surgery regardless of who — team doctor or non-team doctor — performs the surgery:

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Agreement, 2006-2012, p. 197.

³⁴³ Ibid.

³⁴⁴ Ibid.

³⁴⁵ Bill Pennington, "Sports Medicine; Sports Turnaround: The Team Doctors Now Pay the Team," *New York Times*, May 18, 2004, available at [http://query.nytimes.com/gst/fullpage.html?sec=health&res=9501E6D8153FF93BA25756C0A9629C8B63].

A player will have the right to choose the surgeon who will perform surgery provided that: (a) the player will consult unless impossible (e.g., emergency surgery) with the Club physician as to his recommendation as to the need for, the timing of and who should perform the surgery; and (b) the player will give due consideration to the Club physician's recommendations. Any such surgery will be at Club expense; provided, however, that the Club, the Club physician, trainers and any other representative of the Club will not be responsible for or incur any liability (other than the cost of the surgery) for or relating to the adequacy or competency of such surgery or other related medical services rendered in connection with such surgery.³⁴⁶

The condition that requires a player to "give due consideration" to the team physician's recommendations might be open to interpretation. Specifically, this phrase might concern how much discretion a player has, or how much discretion he thinks he has, to select his own surgeon, which could differ from the team's view on how much discretion a player has.

Another issue regarding the medical care provided to players is the potential for a conflict of interest. Some would argue that a team physician, as an employee of the team, might find it challenging to balance the interests of his patients — players with the interests of the coaches, if not the team owners. The following excerpt from a news article describes the issue: "There is a complex tapestry occurring in players' medical treatments. Coaches often want players rushed back onto the field to win games. Players themselves often push to get back quickly. But when some injured players balk, coaches and teammates might consider them loafers and pressure them to return. Coaches pressure doctors for medical releases for players to play. And trainers are often caught in the middle, receiving pressure from coaches and even from owners to influence doctors' decisions."347 A former assistant team physician with the Carolina Panthers, Dr. Walter Beaver, indicated, though, that in his experience, "[y]ou had total authority to take care of the players the way you felt they should be taken care of.... They (team officials) would never question it."348 A team physician for the Pittsburgh Steelers, Jim Bradley, also has asserted that his team's head coach did not intervene in medical decisions. Reportedly, Bradley said: "'If I tell Bill (Cowher, the [former] Steelers coach) a guy can't go, he never gives me any problem.... It's my call." A related issue is the possibility that the premier players on a team receive better medical treatment than other players. During a malpractice suit against a former team doctor, it was "revealed that players believe, in some cases, that star players are treated differently medically than lesser players."350 Reportedly, the executive director of the NFLPA stated: "We never

³⁴⁶ Ibid.

³⁴⁷ Thomas George, "Care by Team Doctors Raises Conflict Issue."

³⁴⁸ Charles Chandler, "Consent at Heart of Lawsuit Facing Panthers, Doctor; Four Ex-Panthers Say Surgeries Went Further Than They Expected," *Charlotte Observer*, p. 1A.

³⁴⁹ Vergano, "NFL Doctors, Players Face Off Over Painful Choices."

³⁵⁰ Thomas George, "Care by Team Doctors Raises Conflict Issue." The player, Jeff Novak, an offensive lineman for the Jacksonville Jaguars, filed a lawsuit against Stephen Lucie, (continued...)

know if it's the patient-doctor relationship or the doctor-owner relationship' that matters in a team's medical decisions."³⁵¹ In 2002, it was reported that the NFLPA and the league were "seeking a uniform standard for the relationships between team doctors and players and to make them more doctor-patient relationships. The league wants players treated effectively and fairly but also wants to protect its teams from expensive liability awards."³⁵² The status of this effort is unclear.

A related issue is the nature of the business arrangement between a team and its medical staff. As described in the following excerpt, some doctors (or their medical practices) pay a team for the privilege of serving as team doctor(s).

In an upside-down scenario spawned by an increasingly competitive health-care market, hospitals and medical practices — eager for any promotional advantage — have begun bidding to pay pro teams as much as \$1.5 million annually for the right to treat their high-salaried players. In addition to the revenue, sports franchises get the services of the provider's physicians without charge or at severely discounted rates. In return, the medical groups and the hospitals are granted the exclusive right to market themselves as the teams' official hospital, H.M.O. or orthopedic group.... Despite concerns among many doctors and the players' unions over the ethics of putting health care out to bid, about half the teams in the four major North American professional sports are now tied contractually to a medical institution.... 353

Criticism is generally not directed at the quality of medical care dispensed, because it is difficult, if not impossible, to ascertain how these marketing arrangements directly affect player treatment. Almost everyone agrees that the pool of sophisticated sports medicine practitioners is so deep that the level of care is likely to be excellent. But the manner in which the doctors and the hospitals are selected and the potential for conflicts of interest bother many people in sports....³⁵⁴

who had been a Jacksonville team doctor, and won a \$5.35 million malpractice award. A news article summarized Novak's story as follows: "[Novak] injured his right knee in training camp on July 28, 1998. Lucie drained blood and fluid from the knee on Aug. 3 in a training room at Alltel Stadium. Two days later, Novak returned to practice, but by Sept. 10 had staph and E-coli infections in the knee and had bleeding episodes. Two operations followed. Novak ... played in only three more games that season, and was not offered a new contract and retired. Lucie testified that he 'had a patient who was in a lot of pain who was having trouble walking around and wanted relief; the best way to provide relief was to remove this pressure and drain the hematoma.' Doctors testifying for Novak said that he should have rested after the surgery, that it was performed in an unsterile environment, that maybe Novak should not have had the surgery at all but should have allowed the knee to rest and heal." (Ibid.)

^{350 (...}continued)

³⁵¹ Vergano, "NFL Doctors, Players Face Off Over Painful Choices."

³⁵² Thomas George, "Care by Team Doctors Raises Conflict Issue."

³⁵³ Pennington, "Sports Medicine; Sports Turnaround: The Team Doctors Now Pay the Team," *New York Times*.

³⁵⁴ Ibid.

Although the medical care provided may not suffer as a result of the business relationship between a team and its team doctor or doctors, concern persists about the appearance of a conflict of interest. Reportedly, Dr. Andrew Bishop, the Atlanta Falcons' team doctor for 11 years, said: "It compromises you as a physician.... The perception is that if this individual was so eager to do this he's willing to pay to do it, then he's going to do whatever management wants to keep the job he paid for."355 Dr. James Bradley, president of the N.F.L. Physicians Society, counters this notion, reportedly saying: "'If you are an N.F.L. team doctor and don't have the best interests of the players in mind ... you are a fool." Reportedly, a spokesman for the NFLPA, Carl Francis, said: "We're always concerned about the relationships between teams and physicians.... But we're willing to give the teams the benefit of the doubt. You would hope that a corporate relationship wouldn't prevent a team from doing the proper research before hiring a medical staff." A final comment on the topic comes from a player, Troy Vincent, then president of the NFL Players Association. Vincent was quoted in a news article as saying: "Our medical care is the only part of our game that isn't regulated.... There are uniform rules on everything else, including how to wear your uniform socks. Shouldn't there be some rules about who gets to treat the players when they're injured? That's when we are most vulnerable, and we should know that the doctor who comes out on that field to help us is the best around, chosen because he is the best, and not for any other reason."358

Workers' Compensation

The NFLPA and the NFL have taken steps to ensure that workers' compensation, which is administered by states, is available to NFL players. The players association has taken steps to ensure that all players are covered by workers' compensation, and "has established a panel of qualified lawyers to help players file and pursue their claims." Similar to other benefits, funding for workers' compensation comes from the portion of the league's total revenues that is allocated to the players. A player may receive both disability benefits and workers' compensation, and the players association and the league have agreed that the disability benefits will not be reduced. The NFLPA has written that it "strongly advises each player to preserve his rights under Workers' Compensation for life-time medical care for his football injuries."

³⁵⁵ Ibid.

³⁵⁶ Ibid.

³⁵⁷ Mike Bianchi, "Doctors, Teams, Players Work in Strange Ways," *Orlando Sentinel*, Sept. 17, 2003, p. D1.

³⁵⁸ Pennington, "Sports Medicine; Sports Turnaround: The Team Doctors Now Pay the Team."

³⁵⁹ Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 4; NFL Players Association, "NFLPA White Paper," p. 21.

³⁶⁰ Ibid.

³⁶¹ Ibid.

Since workers' compensation is administered by states, benefits, requirements, and filing procedures may vary by team location. As the NFLPA has noted, "every state has a time limit within which to file a claim, which could be as short as one (1) year from the date of injury."³⁶² Despite the efforts of the NFLPA to publicize workers' compensation benefits, some players might not explore this option until, for example, they retire or one or more disabilities arise, when it might be too late for them to apply. A successful application for workers' compensation benefits might limit a player's options for recourse concerning his team (including the team's medical staff), which might serve as a deterrent to some players. Generally, an individual who files for and receives workers' compensation may not be permitted to file a lawsuit against his employer.³⁶³ Reportedly, the trial of a former team doctor who was sued by a player "showed that workmen's compensation laws and the league's current collective bargaining agreement protect some doctors and teams from litigation unless ... they are independent contractors."³⁶⁴

Possible Courses of Action

The subject of injuries, chronic health problems, disabilities (interpreted broadly), and benefits for former players is a complex one, and involves a variety issues, some of which are discussed in this report. Accordingly, developing possible courses of action is a challenging undertaking, particularly given the interrelationships among different facets and issues.

The next section examines three proposals offered by the NFLPA, while the following section explores other possible options.

NFLPA's Suggestions for Legislative Action

At a hearing in September 2007, the executive director of the players association proposed three legislative options.³⁶⁵ The NFLPA did not discuss how it developed these proposals, including whether the suggestions were based on any data or documentation.

³⁶² NFL Players Association, "CBA: Workers' Compensation Benefits."

³⁶³ Cornell University Law School, Legal Information Institute, "Workers Compensation," n.d., available at [http://www.law.cornell.edu/wex/index.php/Workerscompensation]; Gregory P. Guyton, "A Brief History of Workers' Compensation," *Iowa Orthopaedic Journal*, 1999, available at [http://www.pubmedcentral.nih.gov/articlerender.fcgi? artid=1888620], pp. 108-109; California Department of Industrial Relations, "Division of Workers' Compensation - Employer Information," n.d., available at [http://www.dir.ca.gov/dwc/Employer.htm].

³⁶⁴ Thomas George, "Care by Team Doctors Raises Conflict Issue."

³⁶⁵ U.S. Congress, Senate Committee on Commerce, Science, and Transportation, "Oversight of the NFL Retirement System," statement of Eugene Upshaw, Executive Director, NFL Players Association, unpublished hearing, 110th Cong., 1st sess., Sept. 18, 2007, p. 3.

Establish Federal Standards for Workers' Compensation. NFLPA suggested that the federal government develop federal standards for workers' compensation, which currently is administered by states. The players association argues that the current system "causes the vast majority of hurt workers, not just NFL players, to settle for a lump sum, and give up their rights to lifetime medical care for their injuries on the job."³⁶⁶ Without additional, detailed information about states' workers' compensation systems or programs, including data about the disposition of workers' compensation applications, the extent of the problem raised by the NFLPA is unknown. This suggestion might be interpreted as applying to all employers and employees, and not just the NFL and professional football players, yet it would be helpful to have an explicit declaration of the scope of the suggestion. In any case, whether the suggestion is for the NFL only or for all employers, the implications of such a change could be far-reaching. Another consideration is whether, since states, historically, have been responsible for administering workers' compensation, this is an area in which the federal government would want to intervene. In sum, additional, detailed information is needed in order to assess this proposal.

Permit Unions to Manage Their Benefit Plans. The NFLPA suggested that the Taft-Hartley Act (29 U.S.C. §§141-197) should be changed to allow the players association, if not all unions, to manage their own "plans." It appears that the NFLPA is referring to 29 U.S.C. §186(c)(5)(B), which requires that a plan subject to the act be administered by a board of trustees, and that the union and the employer be represented equally on the board. As with the first proposal, it is unclear whether the NFLPA is suggesting this change for only the NFL-NFLPA retirement plan, or for all negotiated retirement plans. If the NFLPA is proposing that the suggested change to the Taft-Hartley Act apply to all negotiated plans, it is unclear how other unions and employers might respond to the NFLPA's suggestion.

The rationale offered by the NFLPA for amending the Taft-Hartley Act is as follows: "since the NFLPA has been criticized when applications are denied (even though a majority vote of the six trustees is necessary for a decision), and since current players are funding the system, it makes sense for the players to be the ones making the disability decisions." The players association has also said that "allow[ing] the trustees appointed by the NFLPA to have the sole responsibility to decide applications for disability benefits ... [would] avoid deadlocks and expedite payments." 368

Changing the composition of the Retirement Board might not significantly affect the application approval rate, which means that criticism of the NFLPA might not lessen. As the NFLPA executive director noted in his comments regarding this proposal, "the negotiated contribution by employers is fixed and plan actions cannot impose extra liability."³⁶⁹ Thus, the NFLPA does not assert that changing the

³⁶⁶ Ibid., p. 3.

³⁶⁷ Ibid., p. 3.

Letter from Upshaw to Reps. Conyers, Smith, Sanchez, and Cannon, p. 14.

U.S. Congress, Senate Committee on Commerce, Science, and Transportation, (continued...)

composition of the board would result in an increase in overall payments. Furthermore, as mentioned above, the plan counsel testified that the retirement plan is underfunded actuarially. However, one of the suggestions presented below, regarding the Sports Broadcasting Act of 1961, includes a mechanism that, if enacted, might yield additional funds for benefits.

While it might be important symbolically for the board to consist solely of NFLPA representatives, the substantive significance of the second element of the NFLPA's rationale for this proposal — players fund the retirement plan — is not readily apparent. Furthermore, under the proposed arrangement, the NFLPA alone most likely would bear the brunt of criticism about the disability application process, whereas currently both the league and the players association might be viewed as sharing responsibility for the Retirement Board's decisions.

In his testimony, the NFLPA's executive director mentioned "six trustees," which suggests that he was referring to the Retirement Board (the DICC has only two members) when he proposed that the NFLPA choose all of the individuals who make disability application decisions. Giving the NFLPA sole responsibility for the decisions of the Retirement Board would, according to the players association, end deadlocked votes which, in turn, would aid in expediting payments to applicants. Currently, resolving tie votes involves sending the applicant to a medical advisory physician or using arbitration (the arbitration is among the board members; the applicant "is not a party to the arbitration"). Thus, if there are no deadlocks, the application process would end with the board's decision.

Eliminate the Requirement for the Disability Initial Claims Committee (DICC). In his 2007 testimony, the NFLPA's executive director asked Congress to eliminate the requirement to have "an extra level of decision-making in disability decisions." The executive director appeared to be referring to 29 CFR §2560.503-1(h)(3)(ii) and (4), which require a disability plan to have a mechanism for an applicant to appeal an adverse benefit determination, and stipulate that neither the individual who made the adverse determination, nor anyone subordinate to this individual, can hear the appeal. No rationale accompanied the NFLPA's suggestion, although it seems likely that this step would decrease the amount of time needed to process applications.

On the one hand, eliminating a level of review might reduce the cost and duration of the application process as a whole. On the other hand, as the plan counsel, Douglas W. Ell, testified in 2007, "... one man's 'red tape' is another man's due process." ³⁷¹ The application process, as summarized by Ell, is as follows:

^{369 (...}continued)

[&]quot;Oversight of the NFL Retirement System," statement of Eugene Upshaw, p. 3.

³⁷⁰ U.S. Congress, House Committee on the Judiciary, Subcommittee on Commercial and Administrative Law, *The National Football League's System for Compensating Retired Players: An Uneven Playing Field?* statement of Douglas W. Ell, p. 15.

³⁷¹ Ibid., p. 16.

A player seeking disability benefits begins by completing a written application and sending it to the [Retirement] Plan's administration office in Baltimore. The Plan office has a toll-free number that players call to ask questions and get forms, and also has a website for downloading forms. The player is then sent to a nearby physician approved by the Retirement Board for an examination. These physicians are called neutral physicians and they provide a written report.

Disability claims are decided at the first level by a separate committee, the Disability Initial Claims Committee. Since 2002 the Department of Labor has required the existence of this separate committee. If a player is dissatisfied in any way with the decision of the Committee, he has the right to appeal to the full Retirement Board. Players who appeal are sent to a different second Neutral Physician, as required by federal law. If a player is dissatisfied in any way with the decision of the Retirement Board, he has the right to file suit in federal court.³⁷²

Eliminating one level of review — specifically, the DICC — might affect the overall approval rate, which is 42%. Currently, the DICC performs the initial review, and its approval rate is 34%. As discussed above, the second level of review (the Retirement Board) in the current configuration appears to contribute to a higher overall approval rate. If the DICC were eliminated, would the overall approval rate decrease from 42%, stay the same, or increase?

Other Suggestions

Mitigation of Economic Risk. The health of active and former players might have implications for the NFL, the NFLPA, and society as a whole. Relatively healthy individuals and former players who, through their employment, earn sufficient wages to support themselves and their families are less likely to need government benefits and NFL/NFLPA-provided benefits than individuals who are unemployed, underemployed, or suffer from chronic health problems and/or disabilities. Dave Pear is an example of a former player who relies on government benefits and NFL/NFLPA benefits. A former defensive lineman for the Oakland Raiders and the Tampa Bay Buccaneers, Pear receives a \$606 monthly pension payment from the retirement plan and \$2,000 per month in Social Security disability benefits.³⁷³ Medicare has paid most of the costs of his surgeries.³⁷⁴

Since the injuries and medical conditions an active player sustains most likely will have some bearing on his health in retirement, mitigation begins with active players. (The NFL and NFLPA policies on steroids and substances of abuse are examples of efforts to mitigate risk.³⁷⁵) To aid in mitigating the economic risk

³⁷² Ibid., pp. 14-15.

³⁷³ Leahy, "The Pain Game," p. 10.

³⁷⁴ Ibid.

³⁷⁵ National Football League and NFL Players Association, National Football League Policy on Anabolic Steroids and Related Substances 2007; National Football League and NFL Players Association, National Football League Policy and Program for Substances of (continued...)

associated with the health and safety of players, two options are available. A neutral party could conduct a single review, or multiple reviews, of the conditions, terms, policies, and procedures involving player health and safety. Within the federal government, the National Institute for Occupational Safety and Health and the Institute of Medicine (IOM) of the National Academies are examples of two entities that, with appropriate funding, might be able to undertake this initiative.³⁷⁶ Another option for facilitating the mitigation of risk would be to have the Occupational Safety and Health Administration (OSHA) review the working conditions of NFL players, set and enforce standards, and provide education.³⁷⁷

Independent Studies. While the NFLPA has not conducted its own research or written its own articles on medical subjects and related subjects, the NFL has awarded grants for research, and members of the MTBI Committee, and perhaps other NFL committees as well, have written articles on medical subjects. ³⁷⁸ (See **Appendix B** for a list of studies and articles that each entity has sponsored or published. The recipients of NFL Charities grants for MTBI and related research are

Abuse. Substances of abuse include, for example, marijuana and cocaine. The policy also covers the abuse of prescription drugs, over-the-counter medications, and alcohol. (Ibid., p. 1.)

^{375 (...}continued)

³⁷⁶ NIOSH, which is located within the Dept. of Health and Human Services, Centers for Disease Control, "is the federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. (Dept. of Health and Human Services, Center for Disease Control, National Institution for Occupational Safety and Health, "About NIOSH," available at [http://www.cdc.gov/niosh/about.html].) IOM "provides unbiased, evidence-based, and authoritative information and advice concerning health and science policy to policy-makers, professionals, leaders in every sector of society, and the public at large." (Institute of Medicine, "About," available at [http://www.iom.edu/CMS/AboutIOM.aspx].)

³⁷⁷ OSHA, which is part of the Dept. of Labor, "aims to ensure employee safety and health in the United States by working with employers and employees to create better working environments." (Dept. of Labor, Occupational Safety and Health Administration, "OSHA Facts — August 2007," available at [http://www.osha.gov/as/opa/oshafacts.html].)

³⁷⁸ Although the NFL has referred to the MTBI Committee as "the NFL's independent committee on mild-traumatic brain injury," and has noted that the "MTBI Committee will continue to operate as an independent group," it is unclear what is meant by "independent" in these statements. (National Football League, "NFL Outlines Standards for Concussion Management," news release, May 22, 2007, p. 1.) The degree of independence might depend upon, for example, the terms and conditions governing members' service on the committee; whether committee members are compensated in any way for their service; and whether any other committee, office, or individual in or affiliated with the NFL conducts a pre-publication review of articles produced by committee members. At the conclusion of at least one of the articles published by members of the MTBI Committee is a statement that disavows any conflict of interest. The text of the statement is as follows: "None of the Committee members have a financial or business relationship posing a conflict of interest to the research conducted on concussion in professional football. Funding for this research was provided by the National Football League and NFL Charities. The Charities is funded by the NFL Players' Association and League." (Pellman, et al., "Concussion in Professional Football: Players Returning To the Same Game — Part 7," p. 90.)

shown in **Table 17**.) Selecting individuals and organizations that are not affiliated, either directly or indirectly, with the NFL to conduct research on subjects and issues related to player health might provide a fresh perspective while helping to alter the perception, if not the reality, that, as some observers allege, the NFL uses its own research "to justify league practices." The National Institute of Occupational Safety and Health (NIOSH) and the Center for the Study of Retired Athletes (CSRA), University of North Carolina at Chapel Hill, are two organizations that are independent of the NFL and the NFLPA and may have the capability to conduct studies of active and former NFL players. In the early 1990s, the NFLPA asked NIOSH to conduct a mortality study to "investigate the rate and causes of death of National Football League Players." Additionally, as noted above, Dr. Bennet I. Omalu and his co-authors offered to "collaborate with the Mild Traumatic Brain Injury Committee and the NFL in developing and implementing an optimal research program that will address these newly emerging issues." 382

Data: Collection, Quality, and Access. The collection, analysis, and reporting of certain data might serve a number of purposes, such as providing additional, or more complete, information to active players about injuries and possible long-term consequences, and helping the NFL, the NFLPA, and the retirement plan office to identify and remedy possible problems associated with the administration of benefits. Possible options include providing injury surveillance system reports to active players, which could aid them in understanding, for example, the scope and frequency of injuries, which positions are at risk for certain injuries, and why certain protective equipment or safety procedures are necessary for players' safety. Provision of the data (in addition to the two reports that are produced each season) to the NFLPA would make it possible for the players association to conduct its own analysis of injuries.

Suggestions for new data collection efforts include conducting exit interviews with players who are retiring, carrying out a survey of former players, and establishing and maintaining a database on the disposition of applications for disability benefits. Exit interviews might provide information useful to the league, the players association, and the players themselves. An exit interview could cover a range of topics including, for example, reason(s) for retirement, feedback on the nature and quality of health care received as a player, a discussion of health and safety issues (including the player's narrative of injuries sustained), and retirement

³⁷⁹ Peter Keating, "See No Evil? The NFL Won't Face Concussion Facts," *ESPN.com*, Jan. 19, 2007, available at [http://sports.espn.go.com/nfl/columns/story?id=2736505].

³⁸⁰ Information about NIOSH and CSRA is available at [http://www.cdc.gov/niosh/] and [http://www.csra.unc.edu/], respectively.

³⁸¹ Letter from Baron and Rinsky to Woschitz, p. 1.

Omalu, et al., "Chronic Traumatic Encephalopathy in a National Football League Player," May 2006, p. E1003. According to a 2000 news article, the NFLPA had tried to get the NFL to join the players association in asking the Centers for Disease Control to conduct a "comprehensive injury study," but the NFL was not interested. The NFL apparently responded that no such offer had been made by the players association. (Gutierrez, "NFL Injuries; Pain Game.")

plans.³⁸³ One or more surveys of former players could be used to gather information about their health and employment status, and could aid in determining how well existing benefits meet active and retired players' needs. Benefit program evaluation efforts also might be enhanced by a survey of retired players. Considering that the disposition of applications for disability benefits is a sensitive issue,³⁸⁴ detailed, information that shows how many applications were denied, and why, at each step of the LOD application process and at each step of the T&P application process might be useful in explaining how the application process works and why applications were denied.

Ensuring that the information gleaned from the initiatives described above is provided to, at a minimum, active players, former players, the NFL, and the NFLPA could yield several advantages. Active and former players would be better informed about a number of subjects and issues related to health, safety, and benefits; the NFL, the NFLPA, and the retirement plan office would receive feedback about benefits and the administration of benefits; and NFL and NFLPA personnel who deal with health and safety issues would receive potentially significant information about the medical treatment of players, and the health of two groups of former players — those who have just concluded their NFL careers and those who have been retired for a number of years. Additionally, an overarching benefit could be enhanced accountability and transparency as all of the stakeholders would have access to the same information. The actual benefits of such initiatives, and the validity and reliability of the data collected, would depend upon a number of factors, such as the way in which

An exit physical examination might be useful, too, to both the player and the team. The player would have complete documentation of his health, including neurological health, upon the conclusion of his NFL career, and the information could be submitted to the NFL's injury surveillance system, which then might aid in tracking the long-term effects of injuries, if any. NFL teams are responsible for the cost of medical services provided by team physicians. Having team physicians conduct exit physical examinations might increase the cost of such services to the team. A player might be hesitant to submit to an exit examination if the results could possibly affect his ability to purchase health insurance at a reasonable price after the health insurance provided by the NFL and NFLPA expired. Additionally, although an active or former player may request a copy of his medical records and trainer's records during the off-season, perhaps a copy of both sets of records could be provided automatically to a player upon his retirement. (National Football League and NFL Players Association, NFL Collective Bargaining Agreement, 2006-2012, p. 199.) Under Article XLIV, "Players' Right to Medical Care and Treatment," of the CBA, each player is required to undergo a standard minimum pre-season physical examination. The protocol for standard minimum pre-season physical examination, which includes the following, might serve as a model for an exit examination; general medical examination, orthopedic examination, flexibility, EKG, stress test (at physician's discretion), blood test, urinalysis, vision test, hearing test, dental examination, chest x-ray (at appropriate intervals), and x-ray of all previously injured areas. (Ibid., pp. 197, 279-281.)

³⁸⁴ U.S. Congress, House Committee on the Judiciary, Subcommittee on Commercial and Administrative Law, *The National Football League's System for Compensating Retired Players: An Uneven Playing Field?* statement of Douglas W. Ell; letter from Douglas W. Ell, to Rep. Linda Sanchez, Chair, Subcommittee on Commercial and Administrative Law, July 3, 2007; and U.S. Congress, Senate Committee on Commerce, Science, and Transportation, *Oversight of the NFL Retirement System*, unpublished transcript, 110th Cong., 1st sess., Sept. 18, 2007.

information was collected, how respondents were selected, and how survey questions were worded.

Establish an Ombudsman Office. Although the NFLPA does not represent former players, the organization has a Retired Players Department, which "acts to meet players' needs with the right services; continuously communicates and involves players of all ages to create an exclusive fraternity; works collaboratively with other NFLPA departments and Players Inc to give outstanding value to its members; provides leadership, administration, coordination and implementation to serve the needs of retired players and retired player chapters." Active players are represented by the players association, and they select the members of the NFLPA's Board of Player Representatives. (Members of each team elect a player representative and an alternate player representative. Both serve on the Board of Player Representatives.³⁸⁶)

Additional options for involving current and former players in issues of interest to them and for identifying and addressing problems include expanding the membership of each committee involved in health and safety issues and establishing one or more ombudsmen. Opening up committee membership to active players would promote participation by the individuals who have a direct stake in the work of the committees. Furthermore, players might bring a fresh perspective and innovative ideas to the work of each committee. Expanding committee membership in this way might not be feasible, however. Player-members might find it difficult to attend meetings that are held during the season, and their contributions might be limited during discussions that require specialized knowledge. Establishing an ombudsman office in one or more of the following organizations — the NFL, NFLPA, and retirement plan office — would provide an outlet for active and/or former players. In addition to responding to complaints and requests for assistance, an ombudsman office could function akin to an auditor or a government inspector general, identifying and examining issues and problems. Planning for the establishment of an ombudsman office would probably have to address, at a minimum, funding, organizational independence, and the culture of the organization in which it is to be located.

Concluding Observations

Professional football is an immensely popular sport in the United States, yet it exacts a physical toll on the men who play the game. Injuries and health problems sustained by active players run the gamut from sprained knees and ankles to concussions and broken bones, and injuries might have long-term consequences for a player's health. It has been suggested by several studies, for example, that mild traumatic brain injuries might lead to depression or Alzheimer's-like disease. The NFL and the NFLPA, through collective bargaining and other discussions, have

³⁸⁵ NFL Players Association, "Retired Players Department: FAQs," p. 1.

³⁸⁶ NFL Players Association, "FAQs," n.d., available at [http://www.nflplayers.com/user/template.aspx?fmid=181&lmid=237&pid=0&type=c#a1].

created a variety of benefits for retired and active players, including benefits for individuals who are totally and permanently disabled. Additionally, the league has established several committees that deal with health and safety issues, and the players association has its own medical advisor. Organizations not affiliated with the NFL or the players association also have taken steps to provide assistance to former players.

The subject of players' injuries, disabilities, and benefits is a complex one, and, accordingly, there are a host of issues surrounding this subject. Although the number and type of benefits have grown over the years, older retirees, particularly those who played prior to 1982, have fewer benefits available to them than their successors have. Yet, this subset of former players might have the greatest financial and medical needs. MTBI research has been a somewhat controversial issue, because some experts have published articles whose findings do not agree with those of the NFL's MTBI Committee. These issues, and the others discussed above, suggest that there may not be any simple or easy answers to the health problems experienced by active and former players, or to the questions raised about the sufficiency of benefits for retirees in particular. The players association has suggested three legislative options, and it might be possible, for example, to mitigate the risk of playing professional football and to gather data that could be used to educate players, improve the administration of existing benefits programs, and determine the extent of former players' needs.

Appendix A. Glossary

Active Player — "A Player who is obligated to perform football playing services under a contract with an Employer; provided, however, that for purposes of Section 5.1 only, Active Player will also include a Player who is no longer obligated to perform football playing services under a contract with an Employer, but is between the period beginning when his last such contract expired or was terminated for any reason, and ending on the later of (a) the July 15 following the beginning of the period, or (b) the first day of preseason training camp." 387

Affiliate—"means, with respect to a particular Employer, (a) any corporation, other than the Employer, which is a member of a controlled group of corporations (within the meaning of [Internal Revenue] Code [of 1986, as amended] section 414(b) of which such Employer is a member, (b) any trade or business, other than the Employer, which together with such Employer are under common control (within the meaning of [Internal Revenue] Code section 414(c)), (c) any employer, other than the Employer, which is a member of an affiliated service group (within the meaning of [Internal Revenue] Code section 414(m)) of which such Employer is a member, and (d) any other entity required to be aggregated with the Employer under section 414(o) of the [Internal Revenue] Code."³⁸⁸

Annuity Year — The 12-month period beginning April 1 and ending March 31 of the following year.³⁸⁹

Arising out of League football activities — This means "a disablement arising out of any League pre-season, regular-season, or post-season game, or any combination thereof, or out of League football activity supervised by an Employer, including all required or directed activities. [This phrase] does not include, without limitation, any disablement resulting from other employment, or athletic activity for recreational purposes, nor does it include a disablement that would not qualify for benefits but for an injury (or injuries) or illness that arises out of other than League football activities."

Benefit credit — "means the credit in Section 4.1 [of the Retirement Plan] for the corresponding Credited Season." ³⁹¹

Credited season — "[A] Plan Year in which a Player: (a) is an Active Player (including an injured Player who otherwise satisfies the definition of 'Active Player') on the date of three or more Games, not including Game dates when he was on the Future List; (b) after April 1, 1970, is injured in the course and scope of his

³⁸⁷ Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 2.

³⁸⁸ Ibid.

³⁸⁹ Information provided telephonically by Benjamin L. Zelenko, Esq., to the author on Dec. 10, 2007.

³⁹⁰ Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 26.

³⁹¹ Ibid., pp. 2-3.

employment for an Employer and by reason of such injury receives payment equivalent to his salary for three or more Games or for a number of Games which, when added to the number of Games in such Plan Year for which he otherwise has credit, totals three or more; (c) after reporting to at least one official pre-season training camp or official practice session during such Plan Year, (1) dies, (2) becomes totally and permanently disabled under Section 5.1(a) [active football] or Section 5.1(b) [active nonfootball], or (3) incurs a disability that subsequently qualifies for a benefit under Section 6.1 [line-of-duty disability]; (d) is absent from employment by an Employer while serving in the Armed Forces of the United States, provided such Player returns as an Active Player, after first being eligible for discharge from military service, by the later of (i) 90 days or any longer period prescribed by applicable law, or (ii) the opening of the official pre-season training camp; (e) effective June 1, 2003, was absent from employment by an Employer while serving in the Armed Forces of the United States during the periods set forth in the table below [the periods cover World War II, the Korean War, and the Vietnam War] if (1) during the one year period ending on the date he entered the Armed Forces, such Player either played professional football for an Employer or signed a contract (or a similar document) stipulating his intent to play professional football for an Employer, and (2) such Player was alive on the date set forth in the table below for the corresponding period ... provided that Credited Seasons under this Section 1.10(e) [definition of "credited season"] will be granted only if and to the extent necessary for such Player to become a Vested Player; or (f) effective April 1, 2001, has a season with at least eight games on the practice squad in a Plan Year (either before or after April 1, 2001) in which he did not otherwise earn a Credited Season, provided that he is otherwise vested and earns a Credited Seasons in 2001 or later. A player may earn a maximum of one Credited Season under this Section 1.10(f) regardless of the number of seasons in which he has at least eight games."392

Disability Initial Claims Committee (DICC) — This committee, which has two members (one is appointed by the NFLPA, the other by the NFL Management Council), is "responsible for deciding all initial claims for any and all disability benefits under [the Retirement] Plan. The Disability Initial Claims Committee also will make initial decisions under Sections 5.3 [total and permanent disability] and 6.3 [line-of-duty disability] as to whether Players currently receiving disability benefits should continue to receive those benefits. At the request of a member of the Disability Initial Claims Committee, the Disability Initial Claims Committee will reconsider any decision it has made. When making the decisions described in this [section], the Disability Initial Claims Committee will have full and absolute discretion, authority and power to interpret the Plan and the Trust." 393

Employee — "[A]n individual who (a) is employed by an Employer as an Active Player, or (b) is employed by an Employer or an Affiliate in a capacity other than as

³⁹² Ibid., pp. 3-4.

³⁹³ Ibid., pp. 31-32.

an Active Player (provided that such employment immediately precedes or immediately follows, without interruption, employment as an Active Player)."³⁹⁴

Employer — "A member club of the League." ³⁹⁵

Final League Year — is "the League Year which is scheduled prior to its commencement to be the final League Year of the Collective Bargaining Agreement."³⁹⁶

Inactive vested player — See "vested inactive player."

League Year — is "the period from February 20 of one year through and including February 19 of the following year, or such other one year period to which the NFLPA and the [NFL's] Management Council may agree."³⁹⁷

Life only pension — "Equal monthly pension payments payable during the Player's lifetime only." ³⁹⁸

Line of Duty Disability — "Any player who incurs a 'substantial disablement' (as defined in Section 6.4(a) and (b) [of the *Bert Bell/Pete Rozelle NFL Player Retirement Plan*]) 'arising out of League football activities' (as defined in Section 6.4(c) [of the

Bert Bell/Pete Rozelle NFL Player Retirement Plan]) will receive a monthly line-of-duty disability benefit³⁹⁹"

Normal retirement date — "[T]he first day of the calendar month coincident with or next following a Player's 55th birthday." ⁴⁰⁰

Plan Year — "[A] 12-month period from April 1 to March 31. A Plan Year is identified by the calendar year in which it begins." ⁴⁰¹

Player — "Any person who is or was employed under a contract by an Employer to play football in the League and who is or was (a) on the Active List or the Inactive List (as such lists are or have been defined in the Constitution and By-Laws of the League) of an Employer; (b) on an Employer's roster without being on the Active List by reason of injuries sustained in the Chicago Tribune All-Star Game; (c) injured in the course and scope of his employment for an Employer and by reason of such

³⁹⁴ Ibid., p. 4.

³⁹⁵ Ibid.

³⁹⁶ Ibid.

³⁹⁷ Ibid., p. 6.

³⁹⁸ Ibid., p. 13.

³⁹⁹ Ibid., p. 25.

⁴⁰⁰ Ibid., p. 6.

⁴⁰¹ Ibid.

injury paid under such contract for all or part of the Plan Year in which the injury occurs or occurred; (d) on the Move List, or, for the purposes of the benefits provided by Articles 5, 6 and 7, on the Future List of an Employer after April 1, 1970 (as such lists have been defined in the Constitution and By-Laws of the League); or (e) on the Reserve/Physically Unable to Perform or the Reserve/NFI-EL Lists of an Employer (as such lists have been defined in the Constitution and By-Laws of the League)."⁴⁰²

Pre-59ers — The first pension plan, the Bert Bell NFL Player Retirement Plan, was established in 1962, but it was retrospective to only 1959. Players who left football before 1959 — the pre-59ers — were not covered by this plan. 403

Projected total revenues — "[T]he amount of Benefits projected in accordance with the rules set forth in Article XXIV [of the CBA] (Guaranteed League-wide Salary, Salary Cap & Minimum Team Salary." "404

Qualified joint and survivor annuity — "[A] monthly annuity for the life of the Player with a monthly survivor annuity for the life of the Spouse equal to 50% of the amount of the monthly annuity payable during the life of the Player, which benefit will be the Actuarial Equivalent of the life only pension form of benefit"⁴⁰⁵

Retired player — same as former or inactive player. NFL and NFLPA documents define "active player" and the implication is that an individual who does not fall into the active category is inactive.

Retirement Board — "The Retirement Board will be the 'named fiduciary' of the [Retirement] Plan within the meaning of section 402(a)(2) of ERISA [Employee Retirement Income Security Act], and will be responsible for implementing and administering the Plan, subject to the terms of the Plan and Trust. The Retirement Board will have full and absolute discretion, authority, and power to interpret, control, implement, and manage the Plan and the Trust." 406

Salary cap — "[T]he absolute maximum amount of Salary that each Club may pay or be obligated to pay or provide to players or Player Affiliates, or may pay or be obligated to pay to third parties at the request of and for the benefit of Players or Player Affiliates, at any time during a particular League Year, in accordance with the rules set forth in Article XXIV (Guaranteed League-wide Salary, Salary Cap & Minimum Team Salary), if applicable."

⁴⁰² Ibid.

⁴⁰³ NFL Players Association, "History of Retirement and T&P Benefits for NFL Players," p. 1.

⁴⁰⁴ National Football League and NFL Players Association, *NFL Collective Bargaining Agreement*, 2006-2012, p. 7.

⁴⁰⁵ Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 13.

⁴⁰⁶ Ibid., pp. 29-30.

⁴⁰⁷ National Football League and NFL Players Association, NFL Collective Bargaining (continued...)

Substantial disablement — "(a) For applications received on or after May 1, 2002, a 'substantial disablement' is a 'permanent' disability that: (1) Results in a 50% or greater loss of speech or sight; or (2) Results in a 55% or greater loss of hearing; or (3) Is the primary or contributory cause of the surgical removal or major functional impairment of a vital bodily organ or part of the central nervous system; or (4) For orthopedic impairments, using the American Medical Association Guides to the Evaluation of Permanent Impairment (Fifth Edition, Chicago IL) ('AMA Guides'), is (a) a 38% or greater loss of use of the entire lower extremity; (b) a 23% or greater loss of use of the entire upper extremity; (c) an impairment to the cervical or thoracic spine that results in a 25% or greater whole body impairment; (d) an impairment to the lumbar spine that results in a 20% or greater whole body impairment; or (e) any combination of lower extremity, upper extremity, and spine impairments that results in a 25% or greater whole body impairment. In accordance with the AMA Guides, up to three percentage points may be added for excess pain in each category above ((a) through (e)). The range of motion test will not be used to evaluate spine impairments. (b) A disability will be deemed to be 'permanent' if it has persisted or is expected to persist for at least 12 months from the date of its occurrence and if the Player is not an Active Player."408

Totally and permanently disabled — "An Active Player or a Vested Inactive Player, other than a Player who has reached his Normal Retirement Date [age 55] or begun receiving his monthly pension under Article 4 [Retirement Benefits], will be deemed to be totally and permanently disabled if the Retirement Board or the Disability Initial Claims Committee finds that he has become totally disabled to the extent that he is substantially prevented from or substantially unable to engage in any occupation or employment for remuneration or profit, but expressly excluding any disability suffered while in the military service of any country. A Player will not be considered to be able to engage in any occupation or employment for remuneration or profit within the meaning of this Section 5.2⁴¹⁰ merely because such person is employed by the League or an Employer, manages personal or family investments, is employed by or associated with a charitable organization, or is employed out of benevolence."⁴¹¹

Vested player — A player who: "(a) earns five Credited Seasons; (b) earns four Credited Seasons, including a Credited Season after the 1973 Plan Year; (c) earns three Credited Seasons, including a Credited Season after the 1992 Plan Year; (d)

⁴⁰⁷ (...continued) *Agreement*, 2006-2012, p. 7.

⁴⁰⁸ Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 26.

⁴⁰⁹ A definition of "permanent disability" may be found in Article 6, "Line-of-Duty Disability," of the *Bert Bell/Pete Rozelle NFL Player Retirement Plan*: "A disability will be deemed 'permanent' if it has persisted or is expected to persist for at least 12 months from the date of its occurrence and if the Player is not an Active Player." (Ibid., p. 26.) It is unclear whether this definition also applies to the determination of total and permanent disabilities made by the Retirement Board and the Disability Initial Claims Committee.

⁴¹⁰ This definition is the text of Section 5.2.

⁴¹¹ Bert Bell/Pete Rozelle NFL Player Retirement Plan, p. 21.

after the 1975 Plan Year, is an Employee on his Normal Retirement Date; (e) after receiving total and permanent disability benefits under Article 5 [of the retirement plan], is found to no longer qualify for total and permanent disability; (f) is an Employee after the 1975 Plan year and has at least 10 Years of Service (only for the purpose of applying Article 4 [of the retirement plan] or Section 7.3 [of the retirement plan] and not for any other purpose); (g) is an Employee after the 1988 Plan Year and has at least four Years of Service, at least one of which occurred after the 1988 Plan Year and is a Plan Year in which the Employee did not earn a Credited Season (only for the purpose of applying Article 4 [of the retirement plan] or Section 7.3 [of the retirement plan] and not for any other purpose); (h) is an Employee after the 1992 Plan year and has at least three Years of Service, at least one of which occurred after the 1992 Plan Year and is a Plan Year in which the Employee did not earn a Credited Season (only for the purpose of applying Article 4 [of the retirement plan] or Section 7.3 [of the retirement plan] and not for any other purpose); or (i) (1) earned at least four (4) Credited Seasons, the last of which is earned prior to the 1974 Plan Year, and (2) is alive on June 1, 1998 (only for the purpose of applying Article 4 [of the retirement plan] or Section 7.3 [of the retirement plan] and not for any other purpose).412

Vested inactive player — "A Vested Player who is not an Active Player."

⁴¹² Ibid., p. 7.

Appendix B. NFL and NFLPA Studies Concerning Players' Health

The following information was provided by the NFL and the NFLPA, except for the first item in the list. The study sponsor, participant, or author (for example, the MTBI Committee) is identified following the citation.

- Letter from Sherry Baron, M.D., M.P.H., and Robert Rinsky, U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, to Frank Woschitz, National Football League Players Association, Jan. 10, 1994. (NFLPA)
- Ira R. Casson, Elliot J. Pellman, and David C. Viano, "Chronic Traumatic Encephalopathy in a National Football League Player," *Neurosurgery*, Nov. 2006, pp. 1182-1184. (MTBI Committee)
- Kevin M. Guskiewicz, et al., "Recurrent Concussion and Risk of Depression in Retired Professional Football Players," 2006. (NFLPA)⁴¹⁴
- Elliot J. Pellman, "Background on the National Football League's Research on Concussion in Professional Football," *Neurosurgery*, Oct. 2003, pp. 797-798.(MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Reconstruction of Game Impacts and Injuries," *Neurosurgery*, Oct. 2003, pp. 799-814. (MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Location and Direction of Helmet Impacts Part 2," *Neurosurgery*, Dec. 2003, pp. 1328-1341. (MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Epidemiological Features of Game Injuries and Review of the Literature Part 3," *Neurosurgery*, Jan. 2004, pp. 81-96. (MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Repeat Injuries Part 4," *Neurosurgery*, Oct. 2004, pp. 860-876. (MTBI Committee)

⁴¹³ This study was published as correspondence, and the letter notes that the mortality study was conducted at the request of the NFL Players Association. This document is popularly known as the "NFL mortality study."

⁴¹⁴ Guskiewicz, et al., did not publish an article in 2006. The information from the NFLPA appears to be a reference to this article: Kevin M. Guskiewicz, et al., "Recurrent Concussion and Risk of Depression in Retired Professional Football Players," *Medicine and Science in Sports and Exercise*, June 2007, pp. 903-909.

- Elliot J. Pellman, et al., "Concussion in Professional Football: Injuries Involving 7 or More Days Out Part 5," *Neurosurgery*, Nov. 2004, pp. 1100-1119. (MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Neuropsychological Testing Part 6," *Neurosurgery*, Dec. 2004, pp. 1290-1305. (MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Players Returning to the Same Game Part 7," *Neurosurgery*, Jan. 2005, pp. 79-92. (MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Helmet Testing to Assess Impact Performance Part 11," *Neurosurgery*, Jan. 2006, pp. 78-96. (MTBI Committee)
- Elliot J. Pellman, et al., "Concussion in Professional Football: Recovery of NFL and High School Athletes Assessed by Computerized Neuropsychological Testing Part 12," *Neurosurgery*, Feb. 2006, pp. 263-274. (MTBI Committee)
- Elliot J. Pellman and David C. Viano, "Concussion in Professional Football," *Neurosurgical Focus*, Oct. 2006, pp. 1-10. (MTBI Committee)
- Beverly Pitts, "After the Battle: Report on Lives of Former Players," May 1994. (NFLPA)
- Beverly Pitts, "A Study of Players Who Left Professional Football in the 90's," June 2002. (NFLPA)
- Mark Popovich and Beverly Pitts, "Life After Football: A Survey of Former Players" May 1989. (NFLPA)
- Mark Popovich and Beverly Pitts, "Aftermath of an NFL Career: Injuries." (NFLPA) May 1990
- Mark Popovich and Beverly Pitts, "Lifestyle After Football," Spring 1994. (NFLPA)
- Mark Popovich and Beverly Pitts, "Life After Football: Careers and Opportunities," Sept. 1996. (NFLPA)
- Arthur Roberts, "Determinants of Cardiovascular and Respiratory Risk in Elite Professional Football Players," 2004. (NFLPA)
- Thomas Schwenk, et al., "Depression and Pain in Retired Professional Football Players," n.d. (NFLPA)
- Paul Tagliabue, "Tackling Concussions in Sports," *Neurosurgery*, Oct. 2003, p. 796. (NFL)

- David C. Viano, "Report on ProCap Helmet Tests at Biokinetics," Jan. 17, 2002. (MTBI Committee)⁴¹⁵
- David C. Viano and Elliot J. Pellman, "Concussion in Professional Football: Biomechanics of the Striking Player Part 8," *Neurosurgery*, Feb. 2005, pp. 266-280. (MTBI Committee)
- David C. Viano, et al., "Concussion in Professional Football: Brain Responses by Finite Element Analysis: Part 9," *Neurosurgery*, Nov. 2005, pp. 891-916. (MTBI Committee)
- David C. Viano, et al., "Concussion in Professional Football: Comparison with Boxing Head Impacts," *Neurosurgery*, Dec. 2005, pp. 1154-1172. (MTBI Committee)
- David C. Viano, et al., "Concussion in Professional Football: Performance of Newer Helmets in Reconstructed Game Impacts Part 13," *Neurosurgery*, Sept. 2006, pp. 591-606. (MTBI Committee)
- David C. Viano, Ira R. Casson, and Elliot J. Pellman, "Concussion in Professional Football: Biomechanics of the Struck Player Part 14," *Neurosurgery*, Aug. 2007, pp. 313-328. (MTBI Committee)

Planned or Ongoing Studies

In 2007, the NFL stated that studies are in progress or planned for the following subjects (the organization(s) conducting the study or studies are also listed):

- Protective effects of mouthguards, by Biokinetics and Associates, Ltd. 416
- Biomechanical [research], Wayne State University and the University of Göteborg (Sweden).
- Long-term effects of concussions. The organization(s) conducting this study were not identified, although it was noted that "[d]ifferent phases of the study are being managed by different researchers."⁴¹⁷

⁴¹⁵ This article was not published.

⁴¹⁶ Biokinetics and Associates, Ltd., is a Canadian firm that, according to its mission statement, "provides engineered solutions to human impact protection for sports, transportation and defence/law enforcement appplications." (Biokinetics, "Mission," available at [http://www.biokinetics.com/profile index.html].)

⁴¹⁷ In a *New York Times* article dated May 31, 2007, it was reported that the Commissioner of the NFL had said that the MTBI Committee "had just begun its own study 'to determine if there are any long-term effects of concussions on retired N.F.L. players.' Dr. Casson, the committee's co-chair, said that players who retired from 1986 through 1996 would be (continued...)

 Cardiovascular health of active players, NFL's Cardiovascular Health Committee.⁴¹⁸

^{417 (...}continued)

randomly approached to undergo 'a comprehensive neurological examination, and a comprehensive neurologic history, including a detailed concussion history,' using player recollection cross-referenced with old team injury reports. He said that the study would take two to three years to be completed and another year to be published." (Alan Schwarz, "Study of Ex-N.F.L. Players Ties Concussion to Depression Risk," *New York Times*, May 31, 2007, p. C18.) It is possible that this excerpt refers to the same study that the NFL mentioned in its letter to the House Committee on the Judiciary, which is the source for the studies included in this list. Team injury reports may not include all of the concussions that a player experienced, for reasons discussed above regarding financial incentives that may cause a player not to report an injury.

⁴¹⁸ Letter from Goodell to Reps. Convers and Smith, pp. 3-4.

Appendix C. Members of the Mild Traumatic Brain Injury Committee and Retired Player Study Investigators

The following information is current as of October 30, 2007. The position or role that each individual has or fills on the committee is listed first in each entry, following the individual's name and academic degree(s) or certification. Eight committee members are employed by NFL teams; the team is included in the list of each individual's professional affiliations.⁴¹⁹

MTBI Committee

David Viano, M.D., Ph.D. — Co-chair and biomedical engineer; Biomedical Engineer, ProBiomechanics LLC; Adjunct Professor of Engineering, Wayne State University.

Ira Casson, M.D. — Co-chair and neurologist; Assistant Professor of Neurology, Albert Einstein School of Medicine and Long Island Jewish Medical Center.

Ronnie Barnes, ATC — Head athletic trainer, New York Giants. 420

Rick Burkholder, ATC — Head athletic trainer, Philadelphia Eagles.

Henry Feuer, M.D. — Neurosurgeon; Neurosurgeon, Indiana University Medical Center and Indianapolis Neurosurgical Group; Indianapolis Colts.

Mark Lovell, Ph.D. — Neuropsychologist; Director, University of Pittsburgh Medical Center (UPMC) Sports Concussion Program; Associate Professor of Neurological Surgery, University of Pittsburgh. 421

⁴¹⁹ Unless noted otherwise, the sources of information in this appendix are National Football League, "NFL Outlines Standards for Concussion Management," n.d., pp. 4-5; National Football League, "NFL Subcommittee on Mild Traumatic Brain Injury Membership and Affiliations As of October 30, 2007," n.d.

⁴²⁰ ATC is the acronym for "certified athletic trainer." (National Athletic Trainers Association, "The Facts about Certified Athletic Trainers and the National Athletic Trainers Association," available at [http://www.nata.org/consumer/docs/Factsaboutathletictrainers.pdf].)

⁴²¹ Mark Lovell also is the Chairman and Software Developer, ImPACT Applications, Inc., which sells neurocognitive testing software to NFL teams. (ImPACT Applications, "Developers/Clinical," available at [http://www.impacttest.com/contact.php#anc1]; ImPACT Applications, Inc., "Professional Teams," available at [http://www.impacttest.com/currentusers.php?type=proteam].) For additional information on ImPACT, see Peter Keating, "NFL's Concussion Expert Also Sells Equipment to League," *ESPN.com*, Aug. 10, 2007, available at [http://sports.espn.go.com/nfl/news/story?id=2967678].

Joseph Maroon, M.D. — Neurosurgeon; Neurosurgeon, UPMC; Clinical Professor and Vice Chairman, Department of Neurological Surgery, University of Pittsburgh School of Medicine; Pittsburgh Steelers. 422

Joel Morgenlander, M.D. — Neurologist; Professor of Neurology, Duke University Medical Center.

Thomas Naidich, M.D. — Neuroradiologist; Professor and Chief of Neuroradiology, Mount Sinai School of Medicine.

Elliot Pellman, M.D. — NFL Medical Liaison; Member, NFL Injury and Safety Panel, NFL Subcommittee on Cardiovascular Health, and NFL Foot and Ankle Subcommittee; Medical Director, ProHEALTH Care Associates; Associate Clinical Professor of Medicine and Orthopedics, Mount Sinai School of Medicine; New York Jets.

John Powell, Ph.D., ATC — Epidemiologist; NFL Consultant, Injury Studies, Med Sports Systems; Associate Professor, Departments of Kinesiology and Physical Medicine and Rehabilitation, Michigan State University.

Doug Robertson, M.D. — Sports medicine; Indianapolis Colts.

Andrew Tucker, M.D. — Sports medicine; Co-Chairman, NFL Subcommittee on Cardiovascular Health; Member, NFL Injury and Safety Panel; Chief of Sports Medicine, Union Memorial Hospital; Baltimore Ravens.

Joe Waeckerle, M.D. — Emergency medicine; Editor Emeritus, *Annals of Emergency Medicine*; Clinical Professor of Medicine, University of Missouri School of Medicine; Kansas City Chiefs.

Retired Player Study Investigators

The professional affiliations of investigators who are also members of the MTBI Committee may be found above.

Ira Casson, M.D. — Member of MTBI Committee.

⁴²² Information about Joseph Maroon's employment with the Pittsburgh Steelers came from University of Pittsburgh Medical Center, "Joseph C. Maroon, M.D.," available at [http://www.upmc.com/Communications/MediaRelations/UPMCExperts/ByName/M/MaroonJosephC.htm]. Joseph Maroon also is the Chief Medical Officer, ImPACT Applications, Inc., which sells neurocognitive testing software to NFL teams. (ImPACT Applications, "Developers/Clinical," available at [http://www.impacttest.com/contact.php#anc1]; ImPACT Applications, Inc., "Professional Teams," available at [http://www.impacttest.com/currentusers.php?type=proteam].) For additional information on ImPACT, see Peter Keating, "NFL's Concussion Expert Also Sells Equipment to League," *ESPN.com*, Aug. 10, 2007, available at [http://sports.espn.go.com/nfl/news/story? id=2967678].

Kathleen Finzel, M.D. — Chief of Radiology, ProHEALTH Care Associates. [no entry in parentheses for her indicating her role on the committee]

Mark Haacke, Ph.D. — Biomedical engineering; Professor of Biomedical Engineering, Wayne State University; Director of the MRI Institute for Biomedical Research.

Brian Hainline, M.D. — Neurologist; Associate Clinical Professor, New York University School of Medicine; Chief of Neurology, ProHEALTH Care Associates.

Victor Haughton, M.D. — Neuroradiologist; Professor and Chief of Neuroradiology, University of Wisconsin-Madison.

Danielle LeStrange, R.N. — Study coordinator. 423

Mark Lovell, Ph.D. — Member of MTBI Committee.

Joseph Maroon, M.D. — Member of MTBI Committee.

Joe Morgenlander, M.D. — Member of MTBI Committee.

Thomas Naidich, M.D. — Member of MTBI Committee.

Elliot Pellman, M.D. — Member of MTBI Committee.

Chi-Sing Zee, M.D. — Neuroradiologist; Professor of Radiology and Director of Neuroradiology, Keck School of Medicine, University of Southern California.

David Viano, M.D., Ph.D. — Member of MTBI Committee.

⁴²³ No information was provided about Danielle LeStrange's professional affiliations in the NFL's May 22, 2007, news release.

Appendix D. Acronyms

CBA — collective bargaining agreement.

CTE — chronic traumatic encephalopathy.

DICC — Disability Initial Claims Committee.

LOD — line-of-duty.

MTBI — mild traumatic brain injury.

NFL — National Football League.

NFLMC — National Football League Management Council.

NFLPA — NFL Players Association.

T&P — total and permanent.

EXHIBIT 67

NFL

'Permanently disabled', Harrison fighting for benefits NFL took away

Print



BY MICHAEL ROSENBERG

Posted: Wed Jan. 29, 2014

Updated: Tue Jun. 10, 2014



Dwight Harrison played 10 years in the NFL and now suffers from dementia, but he has been repeatedly denied benefits from the NFL that he feels he deserves.

Dwight Harrison played in the NFL for 10 years. Recently, he was terrified of a phone call.

"I was up all night," he told me, "scared to death. At times, I can't even speak. I'm afraid to talk to you."

I am not in the habit of scaring people to death. But Harrison worried he would say the wrong thing. He worried I wouldn't believe him, which is understandable. His story is so absurd, so unfair, that it sounds like a sick joke. But it is not a joke. It is Harrison's life. And here is what happened:

Harrison requested higher disability pay from his NFL retirement plan.

The plan's trustees said no ... and took away his entire pension.

MICHAEL McCANN: Judge rejects \$765 million NFL concussion settlement

Then they charged him for legal fees.

Now Harrison lives alone in Beaumont, Texas, in what he calls "a little FEMA house," because a hurricane wiped out his other one. He is 65. He is on Medicaid now. He is still fighting for the money, and the acknowledgment that he deserves it. But it is not a fair fight. After too many hits to the head, his brain flickers on and off.

"My situation ... sometimes it's bright, sometimes it's dim, and sometimes the light don't come on at all," said Harrison, who in his 10-year career from 1971 to '80 played for the **Oakland Raiders**, **Buffalo Bills**, Baltimore Colts and **Denver Broncos**. "I can't sometimes keep my thoughts. Forgive me, please."

The night before our first talk a few months ago, Harrison's light went on, and he wanted to take advantage of it. He grabbed a recorder that he keeps on a small table next to his old standard-definition television and spoke his thoughts. The next day, a few minutes after he mustered the courage to answer my call, he placed his recorder next to the phone and pushed PLAY.

We will let the trustees of the Bert Bell/Pete Rozelle NFL Player Retirement Plan begin this story. The year was 1993.

There are six trustees on the board at any given time: Three that represent owners, and three that ostensibly represent players. Former players have long grumbled that the board is more interested in protecting owners and the union than helping former players.

Former Bears star Dave Duerson was appointed by the union but publicly doubted that former players were suffering because of football hits. Duerson later committed suicide and was found to have chronic traumatic encephalopathy (CTE), a brain disease commonly linked to concussions. His tragic story seems to epitomize the NFL's concussion problem: Denial for too long, until it was too late.

But in 1993, the trustees examined Harrison's medical records and determined he was "totally and permanently disabled."

We repeat: The trustees said Harrison was "totally and permanently disabled."

They awarded him a \$1,729 monthly disability benefit. They also determined that Harrison had been disabled since Jan. 1, 1984, and awarded him a lump sum of \$184,756 in retroactive benefits.

Still, Harrison felt he deserved more. He had good reasons to believe that. The retirement plan featured four tiers of "total and permanent disability" benefits, depending mostly on how a player was disabled. The trustees put him on the lowest tier. They determined that, while Harrison clearly had serious medical problems, they did not result from playing in the NFL. He disagreed, and his wife sent a letter to the board asking them to reconsider.

In 1994, the trustees again acknowledged Harrison's "total and permanent disability," at age 45 ... but they would not give him more money. Instead, they informed him that his "disorder has its origin in an incident that occurred while you were playing college football, not League football." They also said that his depression was "of recent origin".

Yes, the trustees tied Harrison's health problems to his life before *and* after his NFL career ... but said he was not damaged *during* his career.

SI VAULT: Wives and girlfriends often bear the burden of caring for suffering former NFL players

How did they reach this conclusion? In part, they used Harrison's honesty against him. He had told at least one doctor he was traumatized seeing a teammate suffer a broken neck and paralysis his senior year at Texas A&I (now Texas A&M-Kingsville). That allowed the trustees to trace his problems to his college career, instead of his NFL career.

And of course, it's reasonable to assume that his memory loss, depression and diminished cognitive function got worse after he retired. That enabled the trustees to say his depression was "of recent origin".

Still, there was no debate about his disabilities. Two doctors had confirmed them -- and one of them was appointed by the retirement plan, not by Harrison. The only dispute was what caused him to be disabled.

Harrison appealed. And this is when his case and his savings began to disintegrate.

The trustees argued that he failed to appear for a psychiatrist's examination, failed to respond to requests for counsel, then failed to appear for another examination. The trustees alleged that when a process server approached Harrison, Harrison drove away quickly, did not stop and kept shaking his head, trying to lose the process server.

They said he did not provide financial information. They said he participated in activities that "include socializing with college football teammates at a team reunion, direct participation in real estate transactions and other business activities." They claim he was trying to run a rodeo out of his backyard. They say witnesses described him as a "businessman" who was "interested in anything to make money." They said he missed appointments with their doctors. He also missed two court hearings.

They denied his appeal and suspended his benefits.

Then they filed a counterclaim to recoup everything they had paid him.

In 1994, the trustees again acknowledged Harrison's "total and permanent disability," at age 45 ... but they would not give him more money. Instead, they informed him that his "disorder has its origin in an incident that occurred while you were playing college football, not League football."

The trustees could have denied his request for more money and kept him on the lowest tier. Instead, they basically called him a crook. In 1996, three years after their chosen doctor wrote a withering report detailing Harrison's maladies, the trustees determined that Harrison was "not now totally and permanently disabled."

That makes it sound like Harrison suddenly got healthy, or had been faking it the whole time. Harrison says now that he never received the notices that the trustees sent him. He says communication broke down when his court-appointed attorney left the case. Harrison, who never graduated from college, represented himself in court.

Why would a man ask for increase in disability pay, then hide from the people who can give it to him? The trustees and their lawyers did not seem to consider that a man with serious mental and physical ailments might miss a few appointments.

The trustees argued that Harrison was "unjustly enriched" by \$236,626 -- every last dollar they had paid him. Because Harrison failed to show up in court, the trustees won a default judgment against him. Harrison was ordered to return all his disability payments, along with \$99,112.50 in legal fees.

The total default judgment against Harrison (including interest) was \$352,252.06.

Harrison's average annual NFL salary: \$49,750.

It got worse. Harrison also had a pension, which is separate from disability pay. The trustees determined that his pension was worth \$130,528, and they successfully offset that against the money he suddenly owed them. So they took his pension.

Harrison sued to get his money back. He had another court-appointed attorney, who resigned. Harrison represented himself again. He knew what was happening was wrong, but he did not understand the legal arguments against it. He was not capable of arguing that his pension should have been exempt from any judgments against him, according to the Employee Retirement Income Security Act of 1974. He just attached a copy of his original complaint and stated his case.

A magistrate judge said his motion "simply relies on his pleadings, and therefore is insufficient."

In 2003, the NFL started giving Harrison retirement benefits again. But that was apparently an accident. In 2007, they cut him off again.

Then, in 2011, when the NFL and the Players Association signed a new collective bargaining agreement, they created a \$620 million Legacy Fund for players who retired before 1993. The NFL proudly announced that every player who retired before 1993 would receive at least \$600 per month, "regardless of the form of benefit". It doesn't matter if the player is disabled or healthy, wealthy or poor.

Harrison received a form letter from NFL commissioner Roger Goodell saying he was entitled to Legacy Fund payments. By the league's calculation, a player with Harrison's experience should have received \$1,144 per month from the Legacy Fund. But in 2012 the trustees voted to offset Harrison's Legacy money against the default judgment. So there went his Legacy Fund benefit.

"I had a little faith in the legal system," Harrison said, "and it just crapped on me."

Harrison's current lawyer, Jeffrey Dahl, argues that the trustees had no legal right to touch Harrison's pension, and he is fighting to have it restored. But attorneys for the retirement plan wrote in a court filing last summer that Harrison has "unquestionably already received more than his fair share of benefits." They also wrote: "Harrison's first lawsuit against the Plan nearly 20 years ago exposed him as a fraud."

A fraud?

Dwight Harrison?

"I'm not a doctor," Harrison says. "If you're going to accuse anybody of fraud, charge them, not me."

Yes, the doctors. Harrison gave me access to his medical records but asked me not to quote them directly out of respect for his privacy. They tell a thorough and heartbreaking version of the horror story you have heard about other retired NFL players: post-concussion syndrome, memory loss and ... well, one thing Harrison still has left is pride. He asked me not to go into detail. But I can say this: The records are extremely detailed, and they are painful to read.

The trustees have decided that when several doctors diagnose a man with mental

problems, including memory loss, and that man misses a few appointments, he is a "fraud" who doesn't deserve any benefits or his pension. And if that man has dementia now, he should apply for benefits elsewhere.

Six doctors have reached the same conclusion about Harrison, independent of each other. The first was in 1993. The most recent was in 2008. And in some cases, the doctor was a neutral psychologist chosen with the approval of the trustees.

Also, in 2008, the Social Security Administration confirmed their findings and said his condition was "due to head injury."

It's a pretty convincing case ... unless you really, really don't want to be convinced.

So what is the NFL's response to all this? Well, Mike Miller, the Director of NFL Player Benefits, did not return several calls. The three current league-appointed trustees (executives Ted Phillips of the Bears, Dick Cass of the Ravens, and Katie Blackburn of the Bengals) referred me to the Groom Law Group, counsel to the plan.

Doug Ell, an attorney with Groom, repeated via email his contention that the plan "has been subjected to both fraud and frivolous litigation by Mr. Harrison."

I asked Ell about the six doctors who have examined Harrison, including at least one who was appointed by the league. Did Harrison dupe them?

Ell's response: "I do not know what doctor reports you refer to, when they were written, or what they say."

I sent Ell a 45-page file of medical records -- which, of course, has been in the record of the case. I asked again if he thinks Harrison duped the doctors.

In his response, Ell did not answer that question or even acknowledge the medical records. Instead, he wrote that Harrison lost benefits because he did not take a medical exam.

"Mr. Harrison was explicitly and repeatedly warned of it, and a federal judge even ordered him to attend, and he refused to do so," Ell wrote.

Ell also wrote: "There is a very generous benefit plan for former NFL Players who have dementia. It is called the '88 Plan. You might encourage Mr. Harrison to seek those benefits."

Why would Ell suggest that Harrison apply for the '88 plan, when his firm has argued in court filings, for many years, that Harrison does not have dementia?

Ell's response: "I do not know whether Mr. Harrison currently has dementia. If he does, there are generous benefits. I do not understand why he would not seek those benefits if he does have dementia."

Dahl, Harrison's lawyer, is skeptical about getting '88 Plan benefits, because the trustees have declared he is no longer a participant in the NFL retirement plan.

10/2/2014

To sum up: The trustees have decided that when several doctors diagnose a man with mental problems, including memory loss, and that man misses a few appointments, he is a "fraud" who doesn't deserve any benefits or his pension. And if that man has dementia now, he should apply for benefits elsewhere. After all, the trustees are tired of his "frivolous" actions.

The trustees convinced courts they were right, but Harrison was severely underlawyered. They have taken a few anecdotes about Harrison trying to conduct business, meeting with college teammates and failing to show up for doctor's exams and court appointments, and used them to punish him for two decades.

How do you measure what is left of a broken man?

Harrison's memories are scattered like leaves on a windy day. He recalls watching game film as a player and not remembering that he played in the game. Sometimes he does not even remember all of his injuries.

Harrison was 44 when this fight began. He is 65 now. His battle for benefits has lasted twice as long as his NFL career. He could have lived a more comfortable life, with better medical care, if the NFL had not cut off the payments he deserved.

For Harrison, the pain cuts deeper than the money he lost. The trustees have essentially told him that his life did not happen the way he says it happened.

"They've got it in there that I am a fraudulent person," he says, and is there a worse charge than that?

"Why?" Harrison asked me. "Why in the world are they treating us so bad? You are dealing with some evil people."

He knows that his only hope is through the legal system. But he is worried about showing up in court and hearing the trustees and their lawyers call him a fraud.

"I don't know if I could take it," he says. "You ruined my life."

I didn't realize it when I called, but this story will remove another piece of Dwight Harrison. The stress of defending himself overwhelmed him.

"I'm not going to give another interview," he said. "It was just too much."

EXHIBIT 68

NEW YORK NEWS **POLITICS** ENTERTAINMENT AUTOS

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Still plenty of skeptics after NFL reaches new deal with players to settle concussionrelated lawsuit

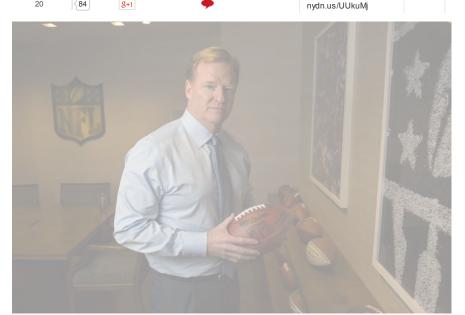
84



BY MICHAEL OKEEFFE

Hopefully the settlement will provide medical care, support and hope to thousands of guys who have suffered because of injuries incurred playing America's most brutal sport at its highest level.

NEW YORK DAILY NEWS / Saturday, June 28, 2014, 11:40 AM AAA SHARE THIS URL



The NFL and commissioner Roger Goodell don't need to admit concussion coverup as part of a new settlement reached last week with thousands of players.



denied his concussion claim in 2001, he says, they told him his blinding headaches, depression and lethargy had nothing to do with the injuries he suffered during his seven years as an offensive lineman for the Minnesota Vikings.

Jim McMahon blasts NFL for not providing 'appropriate care



Dan Marino withdrawing from NFL concussion lawsuit



"Delay, deny and hope they die," is how former Cleveland Browns cornerback Bernie Parrish puts it.

Back then, the NFL was still denying that brain injuries caused long-term health

problem, and Boyd and other former players complained that the disability

program jointly run by the league and its union was designed to stonewall

Brent Boyd has earned the right to be cynical: When the NFL's disability board

So when the NFL and lawyers for the 4,500 former NFL retirees who filed a lawsuit that accused the league of covering up the long-term consequences of traumatic brain injuries submitted a proposed settlement that lifted the cap on concussion-related damages last week, Boyd was skeptical. Will the administrators of this plan also look for ways to deny legitimate claims? Will this deal only benefit the most desperate and leave everybody else hanging?

NFLVIDEO



BY EBENEZER SAMUEL

Stevie Brown expects to be training camp full go

June 25, 2:11PM

BY EBENEZER SAMUEL

With Will Hill gone, Demps could step in as third safety

June 19, 11:51PM

BY EBENEZER SAMUEL



Former NY Giants CB Aaron Ross signs with Baltimore Ravens

VIEW FULL BLOG



players.

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John Madden: NFL announcer gets locker room painkiller



Eight ex-players sue NFL over painkiller abuse

"My fear is that they won't give us any real remedies until we are too sick to know it or we are dead," Boyd says.

This new settlement, the result of six months of negotiations after U.S District Court Judge Anita Brody rejected a deal that capped the NFL's responsibility at \$765 million in January, is hardly perfect. It won't compensate Boyd for income he lost because he's been unable to work for so many years. It won't make whole players who have lost marriages, families and careers because of the physical and emotional pain caused by their brain injuries. It won't bring back men like Junior Seau and others who committed suicide because they could not endure any more suffering.

But it certainly can't be any worse than the cruelty dished out for years by the NFL's disability board, and, hopefully, it will provide medical care, support and hope to thousands of guys who have suffered because of injuries incurred playing America's most brutal sport at its highest level.

"At the end of the day, you can't make the settling defendant do everything you want," says Christopher Seeger, one of the lead attorneys for the players.

Michael Kaplen, a New York attorney who specializes in brain injury issues and teaches at George Washington University Law School, criticizes the proposal because the NFL is not required to acknowledge that it covered up the long-term consequences of concussions for so many years. He says the deal won't help retirees at the low end of the dementia scale who nevertheless have experienced behavioral and emotional problems as a result of brain injuries.

"A mild brain injury is only mild if it is someone else's brain," Kaplen says. "The silent majority of players who have cognitive, emotional, and behavioral impairments because of their reliance on the fraudulent conduct by the NFL will remain uncompensated under this settlement."

Seeger acknowledges that players with comparatively mild symptoms may not qualify for compensation. But they will be eligible for baseline testing, and if their conditions become more severe, they will get paid. "We had to make sure the sickest players were taken care of," he says.

Seeger understands Boyd's fears about stonewalling panels that seem to delight in denying help to suffering people. But he says this proposal, if approved by Brody and the players, will be different. The lawyers will put together a team of independent doctors and administrators that will review claims and make payments. The league will be able to appeal what it believes are fraudulent claims, but this time it won't be running the show.

"I want the NFL to pay for concussion-related injuries and put something new in place for these players, and we did that," he says.

Unfortunately, Roger Goodell will never stand at the 50-yard line at MetLife Stadium and apologize to the players and families who suffered while the NFL and its medical hit men denied the damages of concussions.

But Seeger bristles when people blast the deal because the NFL did not have to acknowledge any wrongdoing. The \$9 billion a year league spoke volumes last week, he says, when it agreed to remove the cap on concussion payments.

"Does anybody," Seeger asks, "think they didn't admit liability with that kind of payment?"

PROMOTED STORIES

June 26, 10:43AM

BY SETH WALDE

Mike Goodson absent at court hearing

June 22, 10:47PM

BY SETH WALDER

Rex Ryan seen at World Cup match

June 19, 12:25PM

BY SETH WALDER



Mike Pettine: Patriots may have had Jets defensive playbook

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EXHIBIT 69



[Print without images]



Friday, January 24, 2014

Lawyers fight over settlement details

By Steve Fainaru and Mark Fainaru-Wada ESPN.com

One week after a federal judge refused to grant preliminary approval of the NFL concussion settlement, the lead negotiator for the players is engaged in an increasingly bitter campaign to beat back opposition to the \$765 million deal.

In conversations and private meetings, Chris Seeger, one of the settlement's main architects, has clashed with his own clients and with attorneys for other players, lobbying for the agreement while lashing out at critics and the media, according to details provided to "Outside the Lines."

Legal experts said the growing fissures among former players and lawyers could undermine the settlement after Judge Anita B. Brody's surprise ruling, which requested more information amid concerns there is not enough money to cover all qualifying players.

To get the settlement approved, proponents will have to convince Brody not only that it provides enough money but also that thousands of former players have enough in common to be legally considered a "class." Several attorneys involved in the case have argued that they don't.

"That's an argument the judge will have to take very seriously," said William Hubbard, a civil litigation expert at the University of Chicago Law School. "Some very famous cases have gone up in flames because of exactly that issue."

In private conversations, several former players have expressed their dissatisfaction to Seeger, their attorney, about the deal; one said he believed that the concussion suit has been "hijacked" by lawyers and that he's expecting a "high number of opt-outs and objections" among Seeger's clients as the settlement moves forward.

On Tuesday, during a meeting of about 60 lawyers at a Manhattan hotel, Seeger was challenged for several minutes by Tom Demetrio, who represents the family of former Chicago Bears defensive back Dave Duerson. One lawyer present described the tense scene as "almost a cross-examination." Seeger angered other lawyers in the informational meeting when he repeatedly deflected questions by citing a "gag order" that he said prevented him from sharing information. The lawyers said they were unaware of any such order.

On Thursday, two days after confronting Seeger, Demetrio filed a motion requesting that Brody direct Seeger and co-lead counsel Sol Weiss to "supply all Plaintiffs' attorneys of record with all of the data utilized by them in reaching the proposed settlement agreement."

Lawyers for former San Diego Chargers great Junior Seau launched their own attack less than 24 hours later, objecting to other aspects of the settlement and citing "serious deficiencies." In a motion filed Friday morning, the lawyers zeroed in on a provision that prevents a player who rejects the deal from pursuing a lawsuit against the

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NFL until the settlement is fully resolved -- possibly delaying cases for years. Seau's lawyers argued that the settlement limits wrongful death claims, suggesting that Seau's children could not collect for the "wrong the NFL did to them."

The challenges are potentially ominous for Seeger and other proponents of the deal, signaling that the families of two prominent players -- Duerson and Seau, both of whom committed suicide by shooting themselves in the chest and were later diagnosed with brain damage -- are considering opting out of the deal.

"This extraordinary settlement could not have been achieved without the contributions of our fellow attorneys, who have been skillful and steadfast advocates for the retired NFL players they represent," Seeger and Weiss said in a statement Friday. "We organized Tuesday's meeting to provide an open forum to discuss the details of the settlement and for lawyers to learn more about how this agreement benefits their clients. There were many productive exchanges, and we are confident that attendees left better equipped to help retired players take advantage of this settlement once it is approved. The retired player community has provided overwhelming support for this agreement, and we look forward to finalizing it soon so they can begin taking advantage of its benefits."

When Brody denied preliminary approval Jan. 14, she ordered negotiators to turn over all data used to come up with a dollar amount for the settlement. The NFL and the players conducted separate analyses, sources familiar with the negotiations said, potentially resulting in different projections on the key question of how many NFL players are likely to get different forms of brain damage.

At the New York meeting, Seeger assured the attorneys in the room that the data existed and that it would reflect that the settlement is sufficient. However, when pressed for details, Seeger referenced the gag order and said his "hands were tied" by Brody. He also surprised many in attendance by announcing that it would be another 30 to 60 days before negotiators are able to refile their motion for preliminary approval -- further delaying a settlement that was announced on the eve of the NFL season.

"New York was a complete and utter waste of time," said one lawyer who attended the meeting. "Nothing, nothing at this informational meeting resembled information. It was a dog and pony show without any dog and without any pony."

Seeger did not respond to an interview request. This week, in an interview with Sports Illustrated writer Peter King, he said he was unconcerned about Brody's ruling and suggested that one reason he pushed the settlement was because he did not think the players had a good case against the NFL.

"I've already settled cases, much bigger than this one," said Seeger, who was co-lead counsel in the class action lawsuit over the pain medication Vioxx, which resulted in a \$4.85 billion settlement. "I've had a good career. My legacy case wasn't going to be a case that didn't work. It wasn't going to be a case that I wasn't totally proud of. Because I know that most of the people involved in this, including the judge, are going to be thought of more for the NFL case than anything else that they will do in their career. That's silly if you ask me, but it's reality."

The players' executive committee -- a select group of lawyers that oversees the negotiations -- already had begun to splinter even before Brody rejected the motion for preliminary approval. Of the six attorneys originally named to the committee, two -- Tom Girardi and Michael Hausfeld -- were kept out of the discussions, according to sources close to the negotiations.

Seeger said he removed Girardi, a Los Angeles-based attorney who has become one of the settlement's main critics, from the negotiating committee because he believed he was leaking information to the media, according to people familiar with the conversations.

Girardi, who says he represents 1,200 former players, complained to "Outside the Lines" last week that he had

7/2/2014 Cases 18-22012 md-Document: Constitute 18-2004 Progress 18-2012 mo input despite his role on the negotiating committee. Seeger has confirmed that in private conversations, the sources said.

Hausfeld was kept out of the negotiations because of his controversial role in a separate case involving proceeds from the NFL's licensing agreements, according to sources close to the case. He remains unpopular among some players but also played a leading role in the concussion suit before he was marginalized.

Like Girardi, Hausfeld has expressed strong reservations about the terms of the settlement.

Seeger and Weiss have clashed with other lawyers on the case. John Giddens, a Jackson, Miss., attorney who represents 240 former players, said he tried to raise questions about the settlement -- including an apparent disparity that awards players without legal representation more money -- on a conference call this month but was shouted down by Weiss.

"In Mississippi, you say your dog's name over and over and they were talking to me like a dog: 'John, John, John, what did we tell you, John?'" Giddens said. "Maybe it's just that these guys are from Philadelphia. I'm so glad we had him on speakerphone, because I was with [attorney] Philip Thomas and another lawyer and we were just looking at each other in disbelief. Here we are on the same side and he's just going off on us."

Shortly after the call, Giddens and Thomas filed a motion on behalf of 177 former players opposing preliminary approval -- the first formal objection to the deal.

When he arrived at the meeting in New York, "I thought there'd be plastic on the floor and walls, like in 'Goodfellas,'" Giddens said. 'These guys, you don't want to piss them off. They're pretty scary dudes. They're used to getting their way. We decided to go against the grain. To hell with pissing them off. We weren't going out like that. We just did what was best for our clients, let the chips fall where they may."

How much the acrimony will affect the suit is unclear. Several lawyers involved in the case said they're waiting for additional information before deciding whether to recommend to their clients to take the deal or opt out.

Asked whether he supported the settlement, one attorney, underscoring his skepticism, said: "I think the settlement is a terrific thing as long as they keep the opt-out provision. This is gonna have a longer shelf life than people think."

EXHIBIT 70







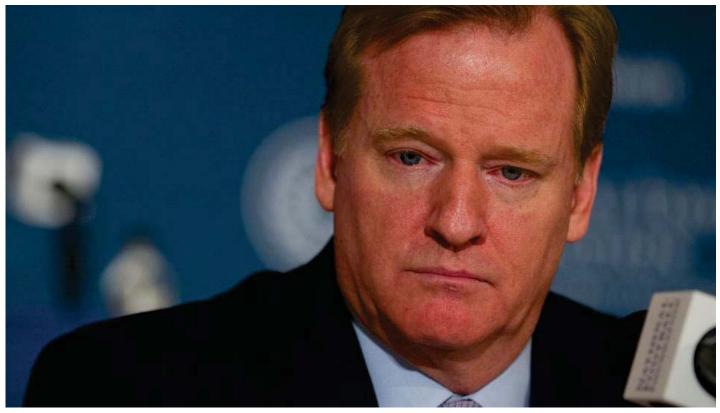


SPORTS ON EARTH



PATRICK HRUBY

SHOW US SOME MATH



NFL commissioner Roger Goodell has defended the league's concussion settlement, but judge Anita B. Brody denied preliminary approval of the plan last week. (AP)

Imagine this: You're in the market for a used car. You go to a dealership, find something promising, sit down with a salesperson. Wary of purchasing a lemon, you ask for a comprehensive vehicle history report.



7/2/2014

Sorry. Not now. You can have it when we close the sale. But trust me, the car runs great!

Er, OK. So, have you at least seen the document yourself?

Nope. The head of the sales department won't share it with me. In fact, I'm not even sure it exists. But trust me, the car runs great!

Sounds sketchy, right? Guess what: All of the above basically describes the proposed settlement of the consolidated National Football League concussion lawsuits. The car is the \$765 million deal, intended to compensate brain-damaged former football players. The dealership salespeople are the top negotiators for both the NFL and the players. And starring in the role of buyer?

The federal judge presiding over the case. The more than 4,500 retired players suing the league. Oh, and many -- seemingly most -- of the attorneys representing those players.

Like I said: things are sketchy.

Last week, judge Anita Brody refused to grant preliminary approval of the settlement, which allocates \$675 million to compensate retired players suffering from neurological diseases and another \$75 million for brain damage diagnosis. Why the red light? To give a go-ahead, Brody has to conclude that the deal is fair, reasonable and adequate -- that the settlement is large enough to cover approximately 20,000 former players over a 65-year span, at least by its own terms.

Right now, she simply doesn't have enough evidence to make that judgment.

On paper, the settlement promises to pay as much as \$5 million to NFL retirees with conditions like Parkinson's and amyotrophic lateral sclerosis (ALS). Former players with chronic traumatic brain injuries that fail to rise to the level of degenerative disease -- think memory lapses, explosive anger, debilitating migraine headaches -- will receive far less. (Read: nothing or close to it). In a motion for approval and supporting documents submitted to Brody, top negotiators for both the NFL and the players claim that the math behind the deal checks out. That medical experts, actuaries and economists have produced "thorough analyses" predicting: (a) how many former football players are brain damaged; (b) what the extent of that damage will be; (c) how much that damage will cost under the terms of the settlement.

The problem? The NFL and players' lawyers didn't provide their analyses to Brody -- essentially asking her to start the vehicle-buying process without giving her a history report. But trust me, the car runs great! In her rejection of the settlement, Brody noted as much:

... even if only 10 percent of Retired NFL Football Players eventually receive a Qualifying Diagnosis, it is difficult to see how the Monetary Award Fund would have the funds available over its lifespan to pay all claimants at these significant award levels

... Plaintiffs allege that their economists conducted analyses to ensure that there would be sufficient funding to provide benefits to all eligible Class Members given the size of the Settlement Class and projected incidence rates, and Plaintiffs' counsel "believe" that the aggregate sum is sufficient to compensate all Retired NFL Football Players who may receive Qualifying Diagnoses. Unfortunately, no such analyses were provided to me in support of the Plaintiffs' Motion ...

Believe it or not, things get sketchier. Shortly after Brody's rejection, attorney Thomas Demetrio - who represents the family of Dave Duerson, a former Chicago Bears defensive back who committed suicide and was later found to have the neurodegenerative disease chronic traumatic encephalopathy (CTE) - told ESPN's Outside the Lines that the players' lead co-counsels, Chris Seeger and Sol Weiss, have operated in a "cloak of secrecy" and that he hasn't seen any analyses, either. "Maybe they don't exist," he said. "Maybe they don't substantiate the \$765 million figure." Meanwhile, attorney Thomas Girardi -- who represents 1,200 former players and was one of the first lawyers to file a concussion suit against the NFL -- told Outside the Lines that he was analyzing the settlement "right now" to see which of his clients would be better off opting out, a number he predicted would be "substantial."

I contacted Demetrio last Thursday. He said the "majority" of the players' lawyers haven't seen any of the settlement's supporting analyses. Two other player attorneys who requested anonymity told me the same thing. One of those attorneys sits on the players' executive committee, a small group of lawyers overseeing negotiations. He said Girardi was "right on." He also said that he didn't think that anyone on the executive committee had seen the analyses -- and even more significantly, nobody saw them before the initial agreement with the NFL was reached last fall, either.

Also last week, I emailed every player lawyer listed on the preliminary approval motion except Seeger and Weiss. I asked five questions, starting with this: *Did you actually see, read and evaluate the analyses before submitting the motion for preliminary approval?* Most didn't answer. Those that did declined to go on the record. Not one said they had seen the analyses.

"In decades of practice," the executive committee attorney told me, "I've never seen a deal done with such cloak."

This matters greatly. For two reasons. First, the documents submitted to Brody claim that the settlement is fair, reasonable and adequate. Specifically, they state:

... after hard-fought negotiations, the Settling Parties arrived at **an aggregate sum that proposed Co-Lead Class Counsel, Class Counsel and Subclass Counsel believe is sufficient to compensate (bold added)** all Retired NFL Football Players who may be diagnosed with Qualifying Diagnoses and their Representative and Derivative Claimants.

If most of the above counsels -- that is, top players' lawyers -- haven't seen the math behind the settlement, then how can they believe it's sufficient? Moreover, why would that make a case in court? Isn't that a bit unethical? Doesn't that pretty much mean they're bulls----ing Brody?

Is bulls---ing a federal judge ever a good idea?

Next point: Similar to Brody, the 4,500-plus former players -- and/or families of deceased retirees -- suing the NFL have a decision to make. Is the settlement fair? Will it take care of their needs? Is the money enough? Or should they opt out of the agreement, and continue to fight the league in court for a bigger, better deal?

In order to answer those questions, they need to see settlement's supporting numbers. So do their attorneys. *All* of their attorneys, and not just the ones who negotiated the proposed agreement with the NFL. To continue the used car analogy: if you hired someone to help you find and buy a vehicle, wouldn't you both want to see the history report?

"Because I have not seen the analyses, I don't have a clue as to whether or not they will help me evaluate the fairness of any proposed settlement," Demetrio said. "Will they help me decide if any of my clients should opt out? I don't have a clue."

"Without the numbers, you can't provide your clients accurate information and advice," said another players' lawyer who asked to remain anonymous. "All I can do is look at my 500 people and say, 'my numbers [of players with neurodegenerative diseases] are way above 10 percent. So how the hell is this going to work?""

Believe it or not, things get sketchier still. According to a document submitted to Brody by former federal judge and settlement mediator Layn Phillips, the players' top attorneys planned on presenting a summary of their experts' analysis -- but not until the final settlement hearing, scheduled to take place *after* the player opt-out period.

In used car terms, that's like being handed a vehicle history report as you drive off the lot.

"Unconscionable," said the executive committee attorney.

"You're the lawyers who asked a judge to approve the settlement, and you didn't attach the documents, and now lawyers who are on your own executive committee don't have those numbers, either?" said Dionne Koller, a University of Baltimore law professor. "Plus you're litigating a case of this much importance and this much public awareness? This thing will be torpedoed if they don't come up with the numbers. And by holding them back, they've created a question: do they even have them?

"Is it unethical? There's a fine line between stupid and unethical. As a legal strategy, I'm scratching my head."

Me, too. How could this happen? Four theories:

1. Hubris: According to the executive committee attorney, both Seeger and Weiss and the lead negotiators for the NFL -- league legal mastermind Jeff Pash and outside counsel Brad Karp -- may have believed they could push the settlement through federal court with little resistance. "My clue," the attorney said, "is that there was a high degree of arrogance."

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Assuming that's true, the NFL and the players' top lawyers have miscalculated. While a truly fair, reasonable and adequate settlement is in everyone's interest -- our overloaded judicial system; brain-damaged former players who need medical care and financial help; an image-conscious league that would like to avoid the public relations water-boarding that would accompany prolonged litigation, damaging discovery and the *drip-drip-drip* of news stories pointing out that football can be very bad for the human brain -- a lemon of a deal would be the opposite.

Hurting players would be left to suffer. The NFL would appear even more sociopathic, capping its legal liability without fully addressing the damage left in its industrial wake. Meanwhile, Brody would look like a duty-shirking, rubber-stamping stooge, something no judge aspires to.

As such, it's hardly surprising that Brody wants to see the numbers. The lead negotiators should have known better.

2. The NFL has something to hide: Any complex analysis supporting the adequacy of the settlement ultimately has to answer two simple questions -- what percentage of retired professional football players will end up with neurodegenerative diseases resulting in cash awards, and what percentage will end up with brain damage that doesn't rise to that level but still may qualify for some form of medical monitoring and/or limited assistance by the terms of the settlement? Ten and 30 percent? Five and 20? Whatever the number, it isn't good for the league: *Together We Make Football, and also 2,000 cases of early-onset dementia*.

"What if the data is worse than the public knows, a higher percentage of serious trauma and injury?" said Warren Zola, a Boston College sports law professor. "That could be something that one side does not want released because of an overwhelming negative response."

Speaking of data: We're talking about projections. Risk models. Future figures based on imperfect assumptions, given that football-induced brain damage isn't well-understood and that no one -- not the NFL; not the players' union; not the Centers for Disease Control -- has ever bothered to conduct a rigorous clinical census of the retired player population. Moreover, we're talking about financial projections as well -- how much money the settlement fund will actually pay out to injured retirees based on their diagnoses, age, number of years played in the league and factors that reduce awards or disqualify players altogether. (Diagnosed with depression? No money for you.) What if the settlement's math only adds up because the qualifying diagnostic process deliberately has been engineered to limit or deny the vast majority of claims -- a familiar, all-too-common phenomenon when it comes to health benefits and workers' compensation for former NFL players?

If that's part of what's going on, the league's lawyers may not be the only ones with something to hide.

3. The players' lawyers are covering their tails: Let's get a little more conspiratorial. Could it be that all or most of the top players' lawyers saw the settlement's math and knew it was somehow shaky. In the interest of expediency and a nice guaranteed payday -- thanks to a settlement-mandated, NFL-funded \$112 million legal fee fund -- they nevertheless decided to roll the dice and see if Brody would fall for an okey-doke.

Now that the judge has called their bluff -- in embarrassing public fashion, no less -- they're covering up. Claiming they've been kept in the dark. Throwing Seeger and Weiss under the bus. And why would they do that?

"To reassure their clients," Zola said.

Consider: Girardi told Outside the Lines that the settlement might not make financial sense for many of the former players he represents *after* Brody rejected the deal. Not before. If the numbers don't work, why did he wait so long to either (a) run them; (b) speak up?

4. The players' lawyers are fighting for more money: Follow me down the rabbit hole. The NFL wants the concussion lawsuits resolved as soon as possible -- otherwise, why settle in the first place? Seeger and Weiss know this. They know the league doesn't want any football brain damage statistics made public. They also know that the Super Bowl is coming up.

Timing is everything. Perhaps creating negative headlines and casting doubt on the agreement is part of their overarching strategy -- a way to pressure the league into throwing a few more coins into the cup, the better to seal the deal, shut up squabbling lawyers and make the whole thing go away.

"Maybe you don't attach the numbers knowing full well that judge Brody won't accept it," Koller said. "Now this clouds the Super Bowl,

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continues to drag on, and it becomes 'let's get to a billion and call it a day."

Maybe. Or maybe there's another reason the settlement's main lawyers haven't shown their work. Whatever the case, Brody is right. No more. Phillips, the mediator, says the numbers are sound. Let's see 'em. The court needs to know. Player attorneys need to know. Players themselves need to know -- not just the players suing the league, but *all* retired players, since the settlement covers them, too. Even the public should get a look. After all, we're the ones trying to figure out if our children should play football; if the settlement is inadequate, we'll be the ones picking up ex-player medical bills through Medicare and higher insurance premiums. We deserve to know the costs. We deserve to know the risks. This is a large private settlement with larger public ramifications. It should never be comparable to a sketchy used car deal.

If anything, said sketchiness is a loud and clear signal that the entire deal merits additional scrutiny. Skepticism, too. Negotiations between the NFL and the top player lawyers should be re-examined, both by Brody and a third-party representing the interests of former players who haven't filed suit. Every actuarial assumption should be examined; every medical and economic data point picked apart by independent experts; every part of the agreement subject to a basic question: does this serve the interests of a small group of highly skilled lawyers? Or does it serve the interests of brain-damaged men and their suffering families, people who need appropriate care and recompense? After all, the NFL concussion settlement doesn't cover a 2002 Honda Civic with a funky smell and a flickering CHECK ENGINE light. It covers human lives. *Caveat emptor*. Show the math.

EXHIBIT 71





Print | Close

How to Diagnose a Battered Brain Before It's Too Late

By Neal Emery

High-impact activities like football are known to cause creeping brain damage that can't easily be detected until after death. But promising research may give rise to new methods of diagnosing chronic traumatic encephalopathy.



REUTERS/Jeff Haynes

In 1996, the brain of an alcoholic dwarf circus clown perplexed scientists with a disease normally limited to boxers. Over 15 years of being shot from a cannon at a circus, the clown developed *dementia pugilistica*, or as its 1928 discoverer Harrison Martland called it, "punch drunk." Less than ten years after the publication of a study on that cannon-rattled brain, an autopsy diagnosed deceased NFL Hall of Famer Mike Webster with the same condition, but now called chronic traumatic encephalopathy (CTE). An upswell in public interest and research following this death brought to light the danger that brain injuries present for athletes in all contact sports. A string of suicides and bizarre deaths by professional athletes, primarily football and hockey players, catalyzed a movement of more than 100 athletes to donate their brains for scientific study.

Junior Seau is the most recent athlete to donate his brain. The day after Junior Seau's suicide last

10/1/2014

week, the co-directors of the Boston University Center for the Study of Traumatic Encephalopathy published a paper, titled "Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma," in the medical journal *Brain Imaging and Behavior*. Even though Corsellis first identified the signs of CTE in the brains of boxers in 1973, significant gaps remain in our knowledge of this disease.

Repeated blows to the head -- from football tackles, blasts from a circus cannon or some other trauma -- put the brain at risk for CTE. Although typically associated with concussions or serious head injuries, brains of football players with CTE but without any concussive history demonstrate that repeated, less severe "subconcussive" injuries provide sufficient trigger for this disease. While individual trauma may produce short-term symptoms, the effects of CTE manifest years after the injuries as the disease progresses and the brain breaks down. Yet many athletes with recurrent head injuries evade CTE; it appears repeated head trauma are necessary, but not sufficient, to trigger CTE. Researchers believe that the nature of the head trauma -- and the severity, frequency, and age of the recipient -- may play a role in whether or not CTE develops. But, for now, why the disease overtakes some and spares others remains a mystery.

The answer hides somewhere amidst tangled neurons and wasted brain tissue. During autopsy, scientists diagnose CTE through the pattern of brain decay and the buildup of tau protein. Normally, the tau protein stabilizes the brain cell skeleton. In both CTE and Alzheimer's, two distinct

MORE ON SPORTS INJURY



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How to Fix Sports' Concussion Crisis

diseases, enzymes cause the protein to release from the skeleton and cluster in cells to form neurofibrillary tangles (NFTs). Researchers remain uncertain about the tangles' exact effect on the brain, says Dr. Brandon Gavett, a neuropsychologist at the University of Colorado-Colorado Springs. Unlike Alzheimer's, which is characterized by the even spread of NFTs, in CTE, NFTs cluster around blood vessels and dead tissue. According to Gavett, some researchers hypothesize that damage to blood vessels during head trauma may cause the brain to wither and form NFTs but thus far no mechanism of disease has been proven.

Brain damage associated with CTE triggers crippling psychological effects. Because the disease can only be diagnosed by autopsy, the changes in behavior and mood must be pieced together by interviews with family members after the afflicted person's death. Family members report that their loved ones exhibited problems with learning, remembering new information, and organization. Judgement and impulse control also frequently gave way to aggressive behavior and problems with addiction. Additionally, those affected by CTE frequently became depressed, agitated, and -- in what ultimately takes the lives of many with CTE -- suicidal. On top of these emotional changes, difficulty with balance,

Despite the wealth of symptoms identified, these psychological factors need to be integrated with genetic susceptibility, chemical analysis of blood and cerebrospinal fluid, and brain imaging in order to accurately diagnose CTE in living patients. Possible chemical markers and genetic predispositions for CTE have been identified from research on Alzheimer's disease, and pilot studies show promise for diagnostic MRI and MRS scans as brain imaging technology improves. Late last year, Boston University CSTE began a study of NFL players and non-contact athletes to begin integrating these parts and develop methods to diagnose CTE before death. Some knowledge needed for such a diagnosis still evades researchers, but scientific advancement creeps closer to this goal every day.

Over the last 7 years, the exponential eruption of public interest and outrage around chronic traumatic encephalopathy has dwarfed the incremental advancements in research. Tremendous holes remain in what we know about how and why CTE develops in battered brains. These questions should not serve as grounds for the public health hazard's dismissal, but should instead prompt caution with a still unfamiliar threat.

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EXHIBIT 72

Long-Term Consequences: Effects on Normal Development Profile After Concussion

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KEYWORDS

- Concussion Development
- Chronic traumatic encephalopathy
- Postconcussion syndrome Youth

In the United States, approximately 1.7 million people sustain a traumatic brain injury (TBI) annually; these injuries account for 1.365 million emergency room visits and 275,000 hospitalizations each year. The majority of these TBIs are minor, with 75% of these injuries classified as mild TBIs (mTBI) or concussions. These numbers

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may, however, vastly underestimate the total incidence of concussion, as many individuals suffering from mild or moderate TBI do not seek medical advice, especially in the 81% to 92% of cases when the concussion is not accompanied by loss of consciousness. Beyond the burden of the injury itself, these TBIs have significant direct and indirect economic consequences, estimated at more than \$60 billion annually in the United States alone.

A concussion is a brain injury caused by a force transmitted to the head from a direct or indirect contact with the head, face, neck, or elsewhere, which results either in a collision between the brain and skull or in a strain on the neural tissue and vasculature.^{7,8} This impact or strain is believed to cause the symptoms of concussion through a cascade characterized by abrupt neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, altered glucose metabolism and cerebral blood flow, and impaired axonal function.⁸ Although these injuries are known to cause short-term deficits, the long-term effects of this neuropathologic cascade are less defined.^{9–14}

Clinically the acute signs and symptoms of a concussion are similar in children and adults, and can include physical signs (eg, loss of consciousness, amnesia), behavioral changes (eg, irritability), cognitive impairment (eg, slowed reaction times), sleep disturbances (eg, drowsiness), somatic symptoms (eg, headaches), cognitive symptoms (eg, feeling "in a fog"), and/or emotional symptoms (eg, emotional lability).¹⁵ These deficits are observed in the absence of structural brain damage in diagnostic magnetic resonance imaging (MRI).^{16,17} While the vast majority of these symptoms resolve spontaneously, many others may linger.⁹ In addition, no two concussions have the same presentation or identical outcomes.¹⁸

The specific mechanism underlying neural tissue damage, however, appears to be different in the adult versus the developing brain. While severe TBI has been shown to have both serious and long-term consequences on personality, mood, and cognition, the precise effect of concussions on development has yet to be fully elucidated. Furthermore, immature neural tissue differs from mature tissue in response to injury, in terms of both plasticity and altered developmental trajectory. The structure of the brain, in relation to the skull and its musculature, is also dissimilar in adults and children, leading to different biomechanics and thus different injury profiles. As a result, different presentations and outcomes would be expected in response to a concussion experienced in youth as compared with one experienced as an adult.

LONG-TERM EFFECTS OF POSTCONCUSSION SYNDROME

The symptoms of a concussion may take some time to resolve, resulting in significant long-term burden. When the symptoms of concussion persist as a variety of cognitive, somatic, and behavioral changes, these lingering deficits comprise postconcussion syndrome (PCS).^{17,31–33} PCS is defined by the *International Classification of Diseases, 10th Revision* (ICD-10) as the occurrence within 1 month of injury of at least 3 of the 8 symptom categories listed in **Box 1**.³⁴ The *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revised) (DSM-IV-R) requires the presence of symptoms in at least 3 of 6 categories for at least 3 months after injury in addition to evidence of neuropsychological dysfunction, as outlined in **Box 2**.³⁵ Whether PCS is experienced following an mTBI seems to be dependent on a combination of factors, including premorbid vulnerability, postinjury psychological adjustment, and postinjury changes in brain function.³⁶ While most of these symptoms typically resolve within a few days or weeks following mTBI or other head injury, some individuals suffer from PCS for months or longer and, although studies remain conflicting, it is believed

Box 1

Characteristics of postconcussion syndrome according to the ICD-10

History of head trauma with loss of consciousness precedes symptom onset by maximum of 4 weeks

Three or more symptom categories:

- Headache, dizziness, malaise, fatigue, noise intolerance
- Irritability, depression, anxiety, emotional lability
- Subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment
- Insomnia
- Reduced alcohol intolerance

Preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role

Data From World Health Organization. The ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research. Geneva (Switzerland): World Health Organization; 1993.

that as many as 15% of people with a history of mTBI still suffer from deficits 1 year after injury. 17,37,38

Adults with PCS often initially present with physical symptoms such as dizziness and headache in the first weeks following injury, with psychosocial symptoms such as depression and irritability first appearing up to a month later.³⁹ These findings mimic those of rodent models, which have reported both impaired learning and

Box 2

Characteristics of postconcussion syndrome according to the DSM-IV-R

A history of head trauma that has caused significant cerebral concussion (eq, with loss of consciousness, posttraumatic amnesia, or seizures)

Neuropsychological evidence of difficulty in attention or memory

Three or more symptoms that last at least 3 months and have an onset shortly after head trauma or represent substantial worsening of previous symptoms:

- Fatique
- Disordered sleep
- Headache
- Dizziness
- Irritability or aggression with little or no provocation
- Anxiety, depression, or affect lability
- Changes in personality
- Apathy or lack of spontaneity

The symptoms result in significant impairment in daily functioning that reflects a decline from previous level

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington, DC: American Psychiatric Association; 1994.

depressive-like behavior in mice following mTBI, perhaps mediated by apoptotic cell death. 40–42 In addition, single and repeated concussions in adults have been shown to be correlated with cognitive deficits months following the injury. Executive functioning impairment also appears to persist, with adults who had experienced an mTBI 6 months prior found to have significantly decreased information processing speed. At 1 year after injury, the most common symptoms appear to be a combination of the physical, the psychosocial, and the cognitive, with reports of headaches, dizziness, disturbances of senses, light and noise sensitivity, and various psychiatric symptoms, including depression, anxiety, coping issues, and psychosocial disability. In addition, studies have suggested that women are more likely to develop PCS, in terms of both more symptoms reported and a longer duration of impairment.

Some adults continue to show motor deficits, functional deficits, and persistent depressive symptoms more than 1 year after injury. The data here are conflicting, however, with other studies indicating that neuropsychological deficits appear to resolve by 1 year after injury. These latter studies tend to include all individuals who had been exposed to any mTBI rather than just those who experienced PCS symptoms; as a result, the sample is overly dilute and the resulting lack of association is not surprising. 51–54

Of interest, several studies have looked at how beliefs regarding expected outcome in response to brain injury might influence an individual's risk of developing PCS. One study found that individuals who had suffered an mTBI and who indicated that they believed their symptoms would have serious negative consequences on their lives were significantly more likely to experience PCS at 3 months following the injury. In fact, these beliefs regarding the perceived severity at the time of injury were more predictive of PCS symptoms at 3 months than were the total number of PCS symptoms reported immediately following the injury. Another study evaluating attitudes surrounding injury recovery found that self-ratings of PCS symptoms were positively related to emotion-focused coping strategies and negatively related to problem-focused coping in adults who had experienced an mTBI. These findings suggest that one's attitudes can influence the extent to which a concussion has long-term, persistent effects.

Although PCS is considered to be fully recoverable with proper treatment, suffering from PCS-related symptoms for an extended time may delay an individual's return to work, adversely affect one's quality of life, and result in additional social and economic costs. ^{17,31,45} The deficits caused by these symptoms may also have an indirect long-term effect by exacerbating a preexisting depression or impairing the ability to adequately cope with stress. ^{56–58} In addition, there is some evidence that concussions result in chronic motor and neuropsychological changes over 3 decades following injury ⁵⁹; however, these findings may be attributable to an early-stage neurodegenerative disease associated with concussion, as discussed later.

Although studies and diagnostic criteria of PCS initially reported dissimilar symptoms for adult and pediatric populations, it is now acknowledged that children and young adults report a PCS that is similar to adults and may suffer from the same behavioral, emotional, and somatic difficulties following mTBI. 36,60 Many of these initial studies of youth concussions focused on athletes, as they tend to be at increased risk of experiencing concussions. Although college football athletes report a higher incidence of concussion than high school athletes, it has been reported that high school athletes take longer to recover, based on neuropsychological testing. This finding of increased youth susceptibility to PCS has been extended to other sports and activities, and is perhaps explained by the fact that the frontal lobes do

not fully develop until late adolescence. 43 Rodent models have also suggested that the immature brain is more susceptible than the adult brain to apoptosis following mTBI.^{62,63} In fact, one prospective cohort study found that age at the time of injury and extent of extracranial injury were the two strongest independent predictors of functional outcome at 6 months after injury. 64 Even in young adults well enough to enroll and continue in college, there is evidence that PCS symptoms may last for years, and that there may be gender differences in PCS resolution, with women reporting more lingering mood and anxiety symptoms. 65

Children differ significantly from adults and adolescents not only in size but also biomechanically, pathophysiologically, neurobehaviorally, and developmentally.²⁸ Because the developing brain is more plastic than the mature brain, younger age at the time of injury was originally thought to have a beneficial effect on recovery and expected outcome. 66 However, current literature indicates that this is not the case; the developing brain appears, in fact, to be more vulnerable to diffuse brain injury, Traumatic injury to the immature brain results in a prolonged period of pathogenesis in both cortical and subcortical structures, leading to progressive neurodegeneration, hyperactivity, and sustained cognitive impairments. 67,68

Although early studies showed either a small or no effect of head injuries on the developing brain, many of these studies had flawed designs; less than half of the 56 studies reviewed by Satz and colleagues^{69,70} from 1970 through 1998 met even 4 of the 6 following recommendations for methodologically sound studies: (1) the inclusion of control groups (either with no injury or with other body injury); (2) the use of a longitudinal design with follow-up assessment post injury; (3) a clear definition of mild injury, without the inclusion of children with more severe injuries; (4) the inclusion of at least 20 children with mTBI; (5) the use of standardized tests to measure outcomes; and (6) controls for preinjury risk factors.

The most methodologically sound studies have found that children report worse cognitive symptoms more than 1 year after concussion than adults. These deficits are first reported months after the original injury and affect the child's school work or abilities to function at home. 71 Children aged 6 to 12 years with mTBI have impaired executive functioning and attention 1 year after injury compared with noninjured controls.72 An mTBI may also cause linguistic changes that adversely affect Verbal IQ and expressive language. Of note, although these deficiencies improved by 6 months after injury, no additional improvement was observed between 6 and 24 months.⁷³ In such cases where symptoms persist, PCS may adversely affect a child's conduct and personality, and can lead to extended school absence and limitations on athletic play. In fact, one study reported that children who showed more PCS symptoms displayed worse overall adjustment in comparison with children with fewer PCS symptoms.³⁶ It has also been suggested that individuals with higher cognitive ability have better outcomes following head injury, because they may be able to recruit alternative and additional neural substrates to compensate for tissue damage. 71,74,75

Although animal models have elucidated the general pathophysiology responsible for acute concussive symptoms, the underlying cause of sustained PCS remains a matter of debate. However, several pathologic mechanisms have been proposed. Some make the pathophysiologic case that a contributing factor for sustained PCS is the microstructural damage of the brain from head injury. Given that the acute injury causes the aforementioned pathophysiologic cascade, it is not unlikely that some of the resulting microstructural damage can persist in some cases and result in the persisting symptoms of PCS sometimes observed. 31 However, as already mentioned for mTBI in adults, the correlation between increased risk of sustained PCS in children with negative coping strategies or beliefs about their mTBI symptoms indicates that there may also be a psychopathologic cause to this long-term PCS. 45,55

This matter is further complicated by various methodologic shortcomings in mTBI and PCS research. These limitations may include retrospective, cross-sectional designs, a lack of appropriate control groups, and a failure to separate different degrees of PCS. 36,39 In addition, studies rely heavily on the self-report of postconcussive symptoms by patients; this has a history of being unreliable, and studies show that a patient's self-report may be the result of simple malingering, an involvement in litigation, or recall biases such as the "good old days" bias, the idea that individuals who sustain an injury often underestimate problems preinjury. 17,77 Finally, whereas PCS is an acknowledged condition, there is a disagreement between ICD-10 and DSM-IV diagnostic criteria; this disagreement emphasizes the confusion over the underlying cause of long-term PCS. Whereas the ICD-10 criteria classifies PCS as symptoms without neuropsychological impairment and focuses instead on premorbid conditions and postinjury psychological adjustment, the DSM-IV criteria do require this neuropsychological impairment and seem to assume that PCS and related symptoms are at least partially caused by an underlying brain trauma.⁷⁸ The variability in diagnostic criteria, and the assumptions about PCS that this variation implies, result in different incidence estimates and limited diagnostic agreement when dealing with PCS patients.79

The enduring effects of PCS appear to be a combination of the biologic, the physiologic, the psychological, and the social. For both the pediatric and adult population, future research that incorporates genetics, advanced neuroimaging, refined cognitive and postconcussive symptom measures, and social environment research can help to achieve an integrated "biopsychosocial" model that may aid in the management of long-term PCS.⁷⁸ This, along with effective education and rehabilitation of patients, will work to reduce the incidence and burden of long-term PCS in TBI patients.

EFFECTS ON BEHAVIOR

Having sustained a previous concussion may alter a child's long-term developmental trajectory years after the symptoms of PCS subside. Studies of PCS typically only follow children for up to 1 year after injury, potentially before the full effects of the injury have manifested themselves. As a result, these studies are unable to measure the extent of the long-term detrimental effects of an mTBI on the developing brain. To properly evaluate the long-term consequences of youth concussion, studies must examine cognitively mature individuals who previously experienced a concussion in their youth.⁸⁰

Because the prefrontal cortex is one of the last brain structures to mature, it is not surprising that parents report attention deficits, hyperactivity, or conduct disorder following a head injury to their child.⁶⁰ In addition, it has been shown that the number of long-term neurobehavioral symptoms in children is related to the severity of the initial mTBI as well as the child's neuropsychological functioning, academic performance, emotional adjustment, and adaptive functioning.^{36,81}

The majority of previous studies examining the effects of brain injuries on development years after the injury have focused on more severe injuries. 82–85 However, these studies of moderate and severe TBI suggest a specific window of time during which the brain may be more vulnerable to injury; TBI experienced in middle childhood and later appears to be less detrimental than injuries sustained earlier. 86–91

One cohort study of 490 children who experienced an mTBI before age 14 years, and who had no prior history of psychiatric illness, found that these children were

significantly more likely to have psychiatric issues in the 3 years following injury than were uninjured controls. The children most commonly presented with attentional problems in the first year following injury. However, there was no difference observed in children who had already had a prior history of psychiatric illness in the year preceding the injury.92

These studies are complicated by the fact that the children more likely to experience concussions were also more likely to have undiagnosed psychiatric issues. To circumvent this issue, some studies have used detailed retrospective questionnaires to assess preinjury psychiatric status. One prospective longitudinal study found that children who experienced an mTBI requiring hospitalization before age 10 years displayed increased hyperactivity/inattention and conduct disorder between the ages of 10 and 13 compared with children who had not experienced an mTBI, as rated both by their mothers and their teachers. 89 This cohort has been followed through age 16, and these issues have been shown to persist. 93 However, these children did not display any deficits in intelligence or academic skills. In addition, children whose injuries did not require hospitalization showed no differences from control children without a history of mTBI. Although there were differences observed in hyperactivity/inattention and conduct disorder based on age at the time of injury (those injured between 0 and 5 years old and those injured between 5 and 10 years old), these differences were not statistically significant.⁸⁹ A later study confirmed these findings and also reported that children injured in preschool had progressively worsening parent and teacher ratings of hyperactivity/inattention and conduct disorder when followed longitudinally from age 7 to 13 years, 80 Another study of 45 adults, with an average age at injury of 8,9 years (standard deviation of 3.3), found that those who experienced posttraumatic amnesia for at least 30 minutes had statistically significant decreases in measures of attention and memory more than 2 decades later. 94 These attentional findings are not surprising, as the prefrontal cortex does not fully develop until late adolescence. In addition, these deficits were not observed in individuals injured as adults. 95

The effects of mTBI on children do not always end with the resolution of PCS, but may have long-term effects on cognitive processing, mood, and behavior. These delayed behavioral impairments suggest the need for continued monitoring and intervention in children, even years after initial concussion.

WHEN TO RETIRE AFTER A CONCUSSION

Following a concussion, the absolute contraindications to return to a contact/collision practice or competition sport include:

- 1. Abnormal neurologic assessment
- 2. Symptomatic of postconcussion signs/symptoms at rest or exertion
- 3. If done, neuropsychological battery not baseline or above
- 4. If done, head computed tomography or MRI shows a lesion placing the athlete at increased risk of head injury (edema, hemorrhage, hydrocephalus, cavum septum pellucidum, arachnoid cyst).

The relative contraindications to return to collision practice or competition include:

- 1. Postconcussion symptoms that last many months and not days
- 2. Mild or indirect blows (whiplash) that produce significant and lengthy postconcussion symptoms.

Thus there are absolute and relative indicators for retirement. Neither are based on a particular number of concussions, but rather on the athlete's response, including duration of symptoms and ease of being concussed. Keeping in mind the increased vulnerability of the developing brain, it is suggested that one might be even more conservative in the under-18 age group as compared with adults.⁹⁶

DEGENERATIVE DISEASE

Brain trauma has long been thought to play a role in initiating or accelerating the molecular cascade involved in several degenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS). ^{97–99} In addition, repetitive concussive and subconcussive brain trauma has been implicated as the primary risk factor for developing the progressive neurodegenerative disease chronic traumatic encephalopathy (CTE), as well as the motor neuron disease variant chronic traumatic encephalomyelopathy (CTE-M). ^{100,101}

Alzheimer Disease

Several epidemiologic studies have found a relationship between head trauma and AD in later life. $^{102-108}$ However, all of these studies based their analyses on a clinical diagnosis of possible or probable AD. Without neuropathologic confirmation of disease, it is possible that other neurodegenerative diseases, such as CTE, were in fact partially or fully responsible for the observed clinical dementia. 109 However, one retrospective study found that individuals with a history of TBI had a higher than expected prevalence of AD pathology observed at autopsy. 110 This result could in part be explained by the fact that β -amyloid precursor protein (APP) is shown to temporarily accumulate in response to acute TBI in genetically susceptible mice; the cleavage of APP results in the β -amyloid (A β) characteristic of AD. 111,112 More research is certainly needed, both to elucidate the relationship between AD and mTBI, and to disambiguate potential cases of CTE from clinically diagnosed cases of probable and possible AD.

Parkinson Disease

TBI has also been implicated as a risk factor for PD. Although the nature of the relationship is poorly understood, animal models suggest that TBI results in α -synuclein deposition, a protein shown to be the primary building block of the Lewy bodies in PD. However, neither animal models nor human studies have conclusively shown a relationship between concussions and the development of PD.

Chronic Traumatic Encephalopathy

CTE is a progressive neurodegenerative tauopathy caused by repeated concussive and subconcussive impacts. Because repeated impacts are thought to be necessary to initiate the disease process, CTE is typically found in those at high risk for experiencing repetitive head trauma, including athletes, those with exposure to injury due to military service or occupation, and individuals who exhibit seizures and/or head-banging behavior. OTE was initially named dementia pugilistica because of its association with the repetitive head trauma experienced by boxers in the ring.

However, head trauma alone is not sufficient to initiate the neuropathologic cascade of CTE. There are many potential risk factors that likely play a role in determining which individuals develop CTE and which individuals do not, given similar head trauma histories. There is some evidence that the ApoE E4 allele may be associated with CTE development. ^{100,101} In addition, the relationship between the development of CTE and the number or severity of head injuries is not yet clear, as some athletes diagnosed with CTE had no reported concussion history despite a history of repetitive subconcussive head trauma. ^{100,101} In addition, the age at which an individual begins

experiencing head injury and the time interval between concussions may play a role in the development of CTE.

Although the disease process likely starts at the time of injury, the initial signs of CTE do not typically manifest until decades later. Therefore, the time course for the presentation of CTE symptoms distinguish it from the cumulative effects of multiple injuries or a form of prolonged PCS. CTE can only be diagnosed post mortem at this time, and as such the precise clinical presentation and the cascade of events preceding it are not yet known. In addition, because the diagnosis of CTE relies on postmortem tissue analysis, the precise epidemiology of CTE is not yet known. Although the majority of professional and collegiate athletes examined for CTE have in fact been found to have had the disease, this represents a biased sample in that families who suspect their loved ones may be impaired are more likely to agree to brain donation for research purposes.

However, CTE is believed to be characterized clinically by a progressive decline of memory and executive functioning; mood and behavioral disturbances that include depression, apathy, impulsivity, anger, irritability, suicidal behavior, and aggressiveness; gait changes that resemble Parkinsonism; and, eventually, progression to dementia. Once this disease process is initiated, the neurodegeneration typically progresses slowly, with a mean survival duration of 18 years following the onset of symptoms. 100,117–119

CTE is characterized neuropathologically by a distinctive pattern of extensive tau-immunoreactive inclusions scattered throughout the cerebral cortex in a patchy, superficial distribution, with focal epicenters at the depths of sulci and around the cerebral vasculature; extensive tau-immunoreactive inclusions in limbic and paralimbic regions as well as brainstem nuclei; and a relative absence of A β deposits. On gross examination, CTE is characterized by generalized atrophy and enlarged ventricles, specific atrophy of the frontal and medial temporal lobes, degenerations of white matter fiber bundles, cavum septum pellucidum often with fenestrations, thinning of the hypothalamic floor, and shrinkage of the mammillary bodies. 100

Although CTE may have similarities with AD, they are two quite distinct diseases. Clinically, CTE typically presents with age of onset in the 40s and 50s as opposed to onset after age 65 years in sporadic AD. In addition, the clinical progression of disease is much slower, often lasting decades, and is characterized by a subtle deterioration in personality and behavior. Neuropathologically both diseases share tau immunoreactivity, but the widespread distribution of neurofibrillary and glial tangles in the frontal, insular, and temporal cortices, white matter, diencephalon, brainstem, and spinal cord is considerably more extensive in CTE than in AD. Furthermore, the pattern of the neurofibrillary abnormalities is entirely distinct from AD or any other tauopathy, especially when considering the absence of the neuritic A β deposits characteristic of AD. However, additional research is needed to better understand the mechanism underlying these changes.

Motor Neuron Disease

Although genetic mutations have been identified that cause ALS, 90% to 95% of ALS cases are sporadic. 121,122 Many risk factors have been identified as possibly contributing to these sporadic cases, but trauma specifically has been implicated as a risk factor that may initiate the molecular cascades resulting in ALS. 199,123 In one case-control study, researchers found that injuries that had occurred in the previous 10 years had the strongest association with diagnosis of ALS. Another case-control study also found that the risk of ALS increased when the last head injury occurred closer to the time of diagnosis. However, other studies have disputed this

association.¹²⁵ On the whole, these findings suggest that head injury may play a role in triggering the onset of motor neuron disease.

Motor neurons in sporadic ALS are often found with TDP-43-immunoreactive inclusion bodies that appear either as rounded hyaline inclusions or as skein-like inclusions; as a result, TDP-43 has been implicated in the pathogenesis of motor neuron disease. 126,127 Widespread TDP-43-positive inclusions have also been found in the vast majority of cases of CTE, and are typically found in the brainstem, basal ganglia, diencephalon, medial temporal lobe, frontal, temporal, and insular cortices, and subcortical white matter. A subset of individuals with CTE also develops a progressive motor neuron disease characterized by profound weakness, atrophy, spasticity, and fasciculations. In these individuals, both tau neurofibrillary pathology and extensive TDP-43-immunoreactive inclusions and neurites were found in the motor cortex of the brain and in the spinal cord in a distribution not characteristic of sporadic ALS.¹⁰¹ Although these initial findings merit further investigation, the co-occurrence of widespread TDP-43 and tau proteinopathies in CTE suggests that repetitive head injury might be associated with the deposition of two abnormally phosphorylated, misfolded proteins, and that in some individuals the TDP-43 proteinopathy is associated with the development of a motor neuron disease.

IMPLICATIONS ON ATHLETIC PARTICIPATION

As a result of these potential long-term consequences, both the incidence and the severity of youth concussion must be reduced. There are several approaches worth evaluating toward this end.

One potential solution involves the development and introduction of better equipment (eg, helmets and mouth guards) that are specifically designed to attenuate the forces associated with concussions. However, although helmets have been shown to decrease the incidence of facial injury as well as moderate and severe TBI, and mouth guards help protect against dental and orofacial injury, there has been no evidence to date that the newest equipment reduces the incidence of concussions or severity of concussion symptoms.⁵

In addition, when new equipment requirements are introduced into a sport, athletes' behavior often changes, resulting in a riskier style of play reflecting their increased feeling of protection. ¹²⁸ In some cases, this has been associated with a paradoxic increase in concussion incidence within an activity. ¹²⁹

A potentially more fruitful approach would be to limit an athlete's exposure to the impacts that might result in concussion. This goal could be accomplished through several means, such as decreasing the number of contact practices an athlete participates in each week; practice alone is responsible for up to 1500 impacts of 10 g or more for some football players. ¹³⁰ Ivy League colleges have taken the lead and recently began implementing this policy, and it is hoped that others will follow suit. In addition, sport-specific rule changes might help reduce the frequency of unnecessary and dangerous collisions, thereby decreasing the burden of athletic concussion.

In most instances, when concussions are properly treated they are not believed to be associated with any long-term sequelae. Ensuring that individuals receive proper medical care, and are given adequate physical and mental rest during recovery, should ensure that these injuries fully heal. Adopting uniform return-to-play guidelines, such as those already discussed here, would help ensure athletes are not permitted to play too soon.

Along these lines, proper education of athletes, coaches, medical professionals, and the general public is necessary to identify and properly treat concussions. There

are many organizations, such as the Centers for Disease Control and Prevention, the Brain Injury Association, and the Sports Legacy Institute, working to improve concussion awareness and educational outreach.

SUMMARY

While most concussions fully resolve within weeks of the injury, for some these concussions can have serious, long-term effects. Concussed individuals can sometimes experience prolonged PCS, lasting for months or even years, which can result in significant physical, emotional, and cognitive stress. In addition, in children and young adults, months of PCS can adversely affect one's developmental trajectory by keeping students out of class and straining personal relationships. In adults, suffering from PCS for an extended period of time may delay one's ability to return to work, resulting in an additional financial and social burden on the concussed individual.

Once the symptoms of concussion subside, in some cases a prior concussion may also have a lasting effect on behavior. These issues are more common in children, as those who have been concussed are more likely to have symptoms of mood or conduct disorders reported by parents and teachers years after injury. Although these findings may in part be due to undiagnosed mood or conduct disorders in children, which resulted in an original injury, the fact that the prefrontal cortex has not fully developed in these injured children provides an additional explanation of aberrant behavior.

In addition, concussions and subconcussive impacts have been shown to increase the risk of developing degenerative disease, sometimes even decades after the injury. There is a good deal of epidemiologic evidence linking a history of head injury with the development of AD, supported by evidence from animal models in response to acute head injury, but additional work is necessary to separate clinically diagnosed AD from other dementias. TBI has also been linked to PD through transient increases in α-synuclein resulting in an increase in the formation of Lewy bodies. However, the strongest evidence for a direct link between repetitive concussive and subconcussive injury and neurodegenerative disease later in life comes from the study of CTE. Originally found in boxers, CTE has been diagnosed in a wide variety of individuals, all of whom had been exposed to repetitive head injury, be it through participation in athletics, military service, occupational hazards, or some other cause. While the tau diagnostic of CTE may begin to aggregate and form inclusions as early as in the second decade, the first clinical signs of CTE are not typically observed until one's 30s or 40s. CTE presents with cognitive deficits, depression, and behavioral disinhibition, and eventually progresses to full-blown dementia.

Although concussions were once considered relatively benign, mounting evidence indicates that concussions can have long-term consequences, sometimes for years or even decades after the injury. Improved understanding of the risks associated with concussions, and their potentially debilitating consequences, highlights the need for better diagnosis, treatment, and prevention.

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EXHIBIT 73



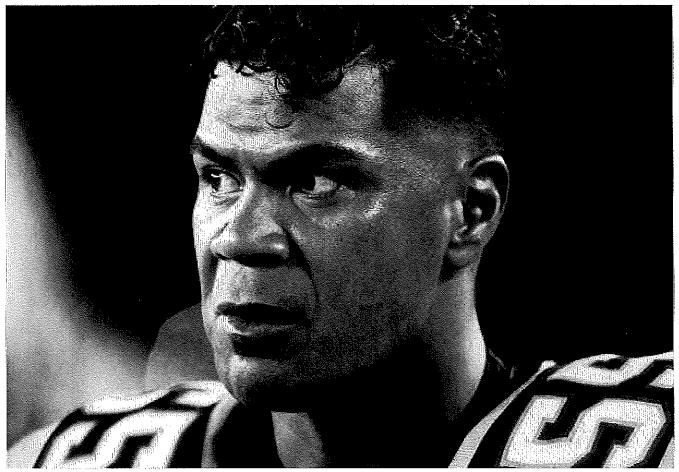
Sports

The Violent Life and Sudden Death of Junior Seau

When the legendary NFL linebacker retired for good in 2010, he seemed set for life: supremely wealthy, beloved across the league, a hero in his hometown of San Diego. Two years later, he was dead. On a lonely morning in a big empty house, Seau shot himself through the chest. It's no longer a secret how much damage pro football can do to the men who play it, but never before had we witnessed it destroy a genuine superstar—not until Junior Seau. in this GQ special report, Seau's friends and former teammates try to make sense of how a life so filled with triumph could go so wrong so fast

BY NATHANIEL PENN

September 2013



average NFL career lasts 3.5 years. Junior Seau, one of the greatest linebackers in the history of the NFL, played for twenty—and San Diego, where he starred most of those years for the Chargers, was his city as much as New York is Derek Jeter's. Seau invested in San Diego both as a businessman and as the head of a foundation serving at-risk kids. But after retiring as a very wealthy man in 2010—he earned more than \$50 million over the course of his long career—he

He withdrew from family and friends. He made terrible business decisions. He abused pills. He drank. He gambled away terrifying sums. It was evident to those who knew him well that he was struggling, but no one foresaw his suicide on the morning of May 2, 2012.

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began to behave uncharacteristically.

The

10/1/2014

Eight months after his death, the scientists who examined his brain announced they had found evidence of CTE (chronic traumatic encephalopathy), a dire neurological disease linked to concussions, which has been a factor in the deaths of many other NFL players. It's impossible to pinpoint the degree to which CTE drove Seau's rapid decline; the disease has been connected to depression, insomnia, emotional withdrawal, and compulsive behavior—all of which afflicted him. But there's one thing everybody close to Seau agrees on: In his final years, Junior was no longer the Junior they had known and loved.



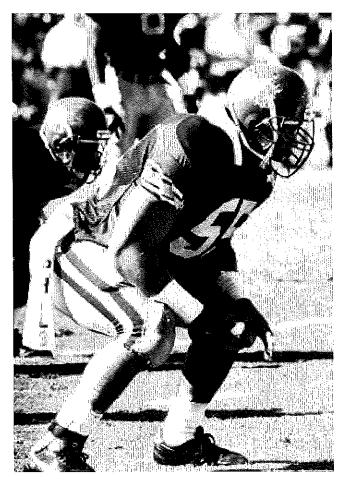
Seau was a star linebacker for twenty seasons, primarily with the San Diego Chargers, where he was legendary for his seeming indestructibility.

1. The Man Who Loved to Hit

Natrone Means (San Diego Chargers running back, exteammate): God Almighty, he was fast. He was strong, man. He was hands-down the best football player I ever played with.

Aaron Taylor (Chargers guard, ex-teammate, friend): Any time you play a sport that requires an ambulance to be onsite, it's inherently a fucking dangerous game, right? "Getting your bell rung" was the euphemism, and I think we all took pride in it. If you didn't light somebody up or get lit up in a collision, there was a sense that we weren't doing our jobs.

Warren Moon (NFL Hall of Fame quarterback, friend): You have two guys running full speed into each other and butting heads. And that's during practice. You don't do anything like that in a game.



Seau at USC with the Chargers.

Jay Michael Auwae (friend): I once asked Junior what the biggest hit was that he could recall. He said, "Buddy, it wasn't in a game. It was in practice. Natrone Means was talking trash; I was talking trash. I said, 'Bring it on!' "Junior said Natrone hit him so hard, and he hit Natrone so hard, that they both were knocked out."

Means: I don't recall this. Maybe it was such a big collision that it's gone from my memory. But I can remember countless times I've seen Junior just smash guys out there. Fights would break out all the time. You want to make a name for yourself. And if you have a name, you want to prove why you have the name.

Taylor: I personally watched him take multiple injections, because he was in front of me in line for them. The 'Caine sisters: Marcaine, lidocaine. Toradol and steroidals to calm down inflammation. I can't say for certain what it was he took, but I would imagine they're not going to give him anything different than what we would've gotten for similar injuries. It was what you did.

Means: I remember him playing in the AFC Championship game [in 1995] with the pinched nerve, man. I mean, sixteen tackles. With a pinched nerve. God Almighty. Never coming out of the game.

Mark Walczak (Chargers tight end, ex-teammate, friend): I couldn't believe the number of surgeries he had. There were like 15 or 16.

Means: It was the "smelling salts and get back in there" generation.

Taylor: You cannot show vulnerability in the locker room. It's despised. Who wants to be a bitch?

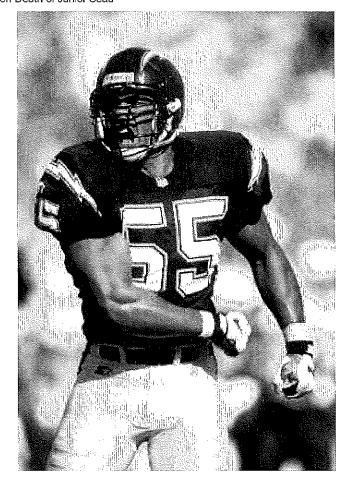
Moon: One thing I read that was peculiar to me—he had now been diagnosed with a concussion. That tells me he

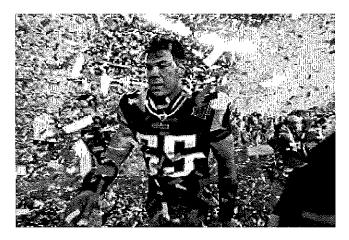
wasn't reporting what was wrong with him. For a guy that played linebacker for twenty years, somewhere in there he would've had a concussion.

2. "What Do You Do with Your Day Now?"

As early as the mid-1990s, when Seau was in his twenties, he was privately complaining of headaches and bouts of dizziness. He also developed insomnia and began to pull away from his wife (they would divorce in 2002) and children. But there were no signs of that man when Seau announced his retirement on August 14, 2006. Instead he struck a more hopeful note: "I'm not retiring," he said. "I am graduating." Just four days later, he changed his mind and signed with the New England Patriots, where for the next four seasons he chased after an elusive Super Bowl ring. In January 2010, a few days before his forty-first birthday, he retired for good. "I'm going to surf," he said.

With his ever present ukulele, Seau was a fixture on the streets and beaches of Oceanside, his suburban San Diego hometown. But soon he began drinking heavily to cope with his insomnia, while also taking Ambien, a sleeping medication prescribed to him by the controversial former Chargers team physician David Chao (who has since, in an unrelated case, been found liable for malpractice). A downward spiral was taking shape: Seau's worsening health affected his business acumen—and when he made bad financial decisions, he would try to gamble his way out of them.





Seau moments after the Patriots' crushing lastminute loss to the Giants in the Super Bowl in 2008.

Taylor: [In 2003] Junior reached out to me. I had retired, and he was thinking of retirement. We had our history together of partying pretty heavily, but he had also watched my transformation. I've been sober eleven years, but [before that] I crashed and burned. So we went for sushi up in Encinitas and talked about the struggles of transition. I was telling him how my first feeling was relief that I didn't have to put my body through that anymore, but very quickly sadness set in. I didn't know what to do. I didn't have schedules; like, I was a blank slate. I had an infinite number of choices, and it was overwhelming and daunting. He expressed some fears of letting go and what's next: "What's it been like? What do you do with your day now? Is it hard?"

Means: If you were to write a script on how to exit the game, Junior's would be an ideal story. The only thing missing was the ring. Coming from the San Diego area, you go up to USC, you come back, and you play for the Chargers. It's almost storybook.

Taylor: The amount of adrenaline and endorphins that is released into our bodies when we run out of a tunnel or make a great play—there's nothing that can replace that [after we retire]. But it doesn't mean that we don't try—and that's where we get into trouble.

Dale Yahnke (Seau's financial adviser): My goal was to make sure that when he retired, he could work as he wanted to, not because he had to. I think we were there. I didn't like seeing him doing things that were destructive. I knew that what he was doing in Vegas was going to end only one way, and I thought it would be humiliating for him. I tried to talk him out of it. He didn't listen. It clearly was accelerating toward the end.

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DID FOOTBALL KILL JUNIOR SEAU?

When a schizophrenic commits suicide, we understand it's his

Auwae: We landed in Vegas one time and immediately, within hours, he won 800-something thousand dollars, okay? So he comes back up to the room. I said, "Let's go home, surf, chill, pay some bills." But after dinner a whale-watcher [a casino handler charged with roping in big-money gamblers] comes up to the room. I'm saying, "June, enough already." And he goes, "No, bro. One more time. I'm gonna clip 'em." Not even two hours later, he comes back up and hits the table with a glass and starts cussing. I was like, "Please don't tell me—" He had lost it all. He's lying on his bed looking at the ceiling, and I go, "Buddy, you gotta stop this, man." He goes, "We got this. We'll get 'em tomorrow." The next morning the whale-watchers show up. June got another half-million dollars, and he goes back down and loses the whole thing.

Taylor: He felt an inordinate amount of financial pressure for a lot of different reasons. He had had some money taken by John Gillette [a San Diego financial adviser who was convicted of stealing millions from his clients]. He had gotten divorced.

Moon: [Seau's The Restaurant, a local institution] wasn't doing as well, because another sports-bar chain had moved in to the same complex, and they were starting to take a lot of his business.

Walczak: He tried to open [another] restaurant in Temecula, which failed. I know that he put his personal guarantee on the restaurant and was continuing to pay the lease when the business was no longer there. Without a doubt his decision-making was impaired.

Auwae: He lost, what, \$1 million trying to do [a chain of] Ruby Tuesdays.

Taylor: He shared with me that there were a lot of demands on him: from friends, family, the community. And it was overwhelming—the calls he would get to help pay \$5,000 for a prom dress or a party or, or, or...

Yahnke: I'll just put it this way—he was very generous. I can't comment on the other side. I have opinions on it, but I can't comment on it.

Taylor: He was a guy from the hood who had made it. He was an icon, and I think because of that, he had a hard time saying no.

disease that really killed him. But did CTE kill Junior Seau? In the brief period of his life after he retired from pro football, he battled alcoholism, insomnia, prescription-drug abuse, depression, and a gambling addiction. Individually, each has been linked to CTE, but in combination the cause-and-effect relationships are impossibly tangled.

As Seau's friend Aaron Taylor observes, "It's a murky pot of gumbo." Russell Lonser, the former chief of surgical neurology at the National Institutes of Health, oversaw the investigation into Seau's brain that confirmed the presence of CTE. But unfortunately that's about all the study told us. "We are just in the infancy of studying CTE," Lonser told GQ. "We don't know if it's progressive or reversible. We don't know the incidence or prevalence or the treatment modalities. Did Junior Seau commit suicide because of CTE? Absolutely no one can answer that."-N.P.

Yahnke: What he needed was for someone to say, "This is destructive behavior, and you need to stop doing it." I tried; didn't work. [The former head of Seau's foundation] tried; didn't work. So I don't know what it would've taken. He has great kids. I would've liked to see him spend more time with them. I think he was conflicted about it. He spent a lot of time at bars and things like that. His foundation helped a lot of kids around San Diego, but why he didn't spend more time with his own kids, who he loved, I don't know. I think deep down, Junior was lonely. He had a lot of what he would call buddies, but I don't think there was anybody that he could truly open up his soul to.

Taylor: Guys keep things to themselves. They suck it up. It allows us to be good football players, but it slices our throats on the back end, because we use the same tools in this new arena that allowed us to be successful during our careers. The alcohol was a numbing-out of all the things that troubled him: He had financial demands, he had familial issues, he had marriage issues. I know he had deep, deep guilt about how he was not showing up as a father toward the end.

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3. From Ali to Urkel

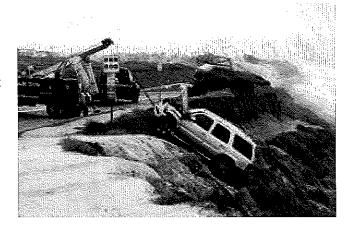
Throughout his career, Seau was the gentlest of men off the field, but after his retirement he sometimes became aggressive and even violent with those close to him. At approximately 12:20 a.m. on October 18, 2010, he was arrested on suspicion of domestic violence after an incident with a girlfriend. Within hours of posting bail, he was involved in a bizarre accident on a coastal road in Carlsbad, California. The story made national headlines.

Walczak: He was up all night with the police. Finally they got it sorted out, and he was driving south, and he told me he fell asleep and drove off the cliff. At that time, I had no reason not to believe him. I wish I'd gone and looked at the site where it happened, because it wasn't an accident. I've been there lots of times, and it just doesn't work. It would be a ninety-degree turn. You'd have to crank the wheel so hard you'd have to time it just so.

Taylor: He was a beaten-down man. His confidence was gone. He seemed worn-out. It was hard for him to articulate coherent thoughts. There was a degradation of the dude that I remember playing with. I played with Muhammad Ali, and I had lunch with a guy that showed up with the machismo of Urkel. He looked like a crackhead walking in off the street. He said, "I need help. I don't know what to do. I'm an addict of a lot of things. Tell me what to do, man."

Walczak: Ambien is a crazy, hallucinogenic, mind-altering, addictive, terrible drug. I think part of his struggles were with that [drug] altering his ability to make sense or judgments. He didn't take it as prescribed; he'd take three over the course of the night.

Jamie Paulin (Nashville songwriter, friend): We'd talk about [a job in] sportscasting, where he'd be like, "Oh yeah, I'm going to get on that," and then the next day there would be no thought of it. It was, like, too much to think about.



Seau, post-retirement, in a harbinger of tragedy to come, Seau drove his car off a beachside cliff but somehow survived the crash.

Auwae: He would forget the phone on the back of the [car's] hood and drive two miles and not know where the phone is. Ukuleles, leaving them in different places. Missing appointments—like [his daughter] Sydney's volleyball game.

Taylor: We went to a meeting of a twelve-step program. He introduced himself as an addict and shared where he was at. I knew how much courage it took, because I know how hard it was for me, and I was a nobody as a player. *Everybody* in San Diego knew what happened with his car. I was very encouraged. But pretty quickly after that, he went dark.

Auwae: We went to a bar in Carlsbad [in late April 2012]. This fan comes up to him: "Mr. Seau, you mind if—" And he's like, "Get the fuck out of here, man." Dude, that's not Junior. This is so not him. I go, "What's wrong with you?" He just said, "I'm tired of it, man."

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4. A Bullet to the Chest

In late April 2012, Walczak spent the week of his fiftieth birthday with Seau. The men spent that week hopping around local restaurants and bars, always returning to Seau's house across the street from the Pacific Ocean. Throughout, Seau regularly requested that they play music together—in particular a song that Paulin had written called "Who I Ain't."



The extended Seau family carries Junior's coffin at his funeralin Oceanside, California.

Walczak: I've suffered many, many concussions, and at certain times I can't remember anything. He cracked on me: "Buddy, do you got Sometimer's or Alzheimer's?" We had cocktails and relaxed near the ocean. He seemed to be really right. We talked about Dave Duerson [the former Chicago Bears All-Pro safety who had shot himself; later he was discovered to have been suffering from CTE], because it came up on ESPN. I asked him: "How do you feel? Do you have symptoms of anything?" He said, "I feel great."

Auwae: Everybody talked about the suicide note; it wasn't a suicide note, it was the lyrics of a song.

Paulin: "Who I Ain't" was written ten years ago by me and Justin Lantz. It's about a guy who has made a lot of mistakes but then finds peace and redemption. Junior was here [in Nashville] that April, and he said, "Oh, you gotta send me a copy of that." We told him the chords and wrote down the lyrics for him.

Walczak: During the course of that week, we probably sang the song together fifty times, getting it right. When he found a song that he liked, man, he'd play it over and over. It goes, Cuz I've broke the hearts of angels, cursed my fellow man / Turned from the Bible with a bottle in my hand **JABSOO** hope for forgiveness, when the good Lord calls my

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name / Is that he knows who I am and who I ain't. Maybe he knew that he was going to end it. Maybe this was his way of being at peace with it and sharing his peace.

Paulin: I never thought he felt he was carrying any unfixable mistakes. Apparently he felt he was.

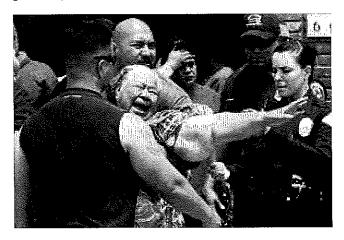
On Tuesday, May 1, Seau sent a group text to family members: "I LOVE YOU." He spent that evening watching a Lakers game on TV with a girlfriend. The following morning, she discovered his body. Among the mysteries of that day: The SIM card from Seau's cell phone was never found. Auwae has speculated that Seau received a collections call from a Las Vegas casino, which may have contributed to his suicide. In any event, Seau's gambling debts were forgiven following his death.

Walczak: He didn't tell me he owned a gun. I do know this: He had probably never, ever fired a gun in his life before.

Mark Malamatos (investigator for county medical examiner's office; from his report): At approximately 0915 hours, [Seau's girlfriend] left her gym and attempted to telephone [Seau] four or five times. When he did not answer, she decided to drive by the gym where he worked out. She then went back to the house, and when she entered through the garage, she had a feeling that it was unusually quiet. When she walked up the steps to the living room/kitchen area, she saw [Seau's] dog, and knew it was unusual for him to be in there. She then walked down the hallway to the master bedroom and did not see [Seau] in bed. She noticed that one of the spare bedroom doors was shut, which again she thought was very unusual. As she walked into the spare bedroom, she saw the decedent lying on the bed.

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Auwae: What's weird about the whole thing is he didn't even kill himself in his room. He went to a spare room. He sat in bed, grabbed the gun, pressed it hard against his chest, and blew a hollow-point round right through himself.



Seau's mother after her son's suicide.

Walczak: It was completely uncharacteristic of a guy who was the constant competitor, the most generous person in the world, the biggest lover of people. It's just strange that his life would end in a way that symbolized uncaring and selfishness and thoughtlessness. He somehow lost his mind.

5. The Life and Afterlife of Junior Seau

In April 2013, the Seau family joined more than 4,400 former players in a mass of lawsuits charging that the NFL and the helmet manufacturer Riddell had misrepresented or suppressed data about the risks associated with concussions. Of the players involved in wrongful-death lawsuits, Junior Seau is one of the youngest. "We know this lawsuit will not bring back Junior," the Seau family said in a statement published by the Associated Press. "But it will send a message that the NFL needs to care for its former players, acknowledge its decades of deception on the issue of head injuries and player safety, and make the game safer for future generations."

Taylor: Junior was different. Junior was special. There's legendary stories of him playing with broken forearms and compound fractures. I don't know if I ever saw him for any reason leave a game. Junior fought through so much pain. There would be times that he wouldn't practice because he couldn't walk, but magically he would show up on Sunday.

Means: I remember when I left San Diego in 1996 and went to Jacksonville. I was thinking, "I guess every NFL team has a Junior Seau linebacker." I'm out there that first day of practice, I'm looking around, I'm like, "Okay, where's the Junior Seau at?" You see a lot of guys who look the part, but I'm like, "Naw, that's not the one.... No, that's not the guy...." That's when it really hit me: "Oh shit. Okay, now I get it."

Auwae: Once he told me about his first gym workout as a rookie. He was nervous about making the team. His dad wanted to buy the house he lives in now, but Junior didn't even have a bank account. At the gym, the most feared guy on the team starts flinging up the weights, and he's struggling. Junior grabbed the same weights and pressed them like nothing. He could feel everybody looking at him, impressed with him. Afterward he went to the phone and called his mom. He goes, "Mom, tell Dad to go buy the house. We're gonna be here for a while."

EXHIBIT 74

MENSJOURNAL

Dave Duerson: The Ferocious Life and Tragic Death of a Super Bowl Star

By Paul Solotaroff May 2011

For years ex-Bear Dave Duerson had a hand in turning down scores of disability claims of retired players — though he likely suffered from brain injuries himself. In February, 2011, he shot himself in the heart. Was it because he couldn't bear to admit his betrayal?

Editor's Note: On May 2, 2011, doctors at the <u>Center for Study of Traumatic Encephalopathy</u> at the Boston University School of Medicine announced that Dave Duerson was suffering from a "moderately advanced" case of chronic traumatic encephalopathy (CTE) – a disease linked to repeated blows to the head whose symptoms can include memory loss, depression and dementia – when he committed suicide three months earlier. 17 months later, after four years of research, Duerson's CTE was confirmed in the scientific journal 'Brain.' In February 2011, Paul Solotaroff and Rick Telander covered Duerson's once-charmed life and sad end.

Dave Duerson set the scene with a hangman's care before climbing into bed with the revolver. The former Pro Bowl safety for the Super Bowl—champion 1985 Chicago Bears drew the curtains of his beachfront Florida condo, laid a shrine of framed medals and an American flag to his father, a World War II vet, and pulled the top sheet up over his naked body, a kindness to whoever found him later. On the dining room table were notes and a typed letter that were alternately intimate and official, telling his former wife where his assets were and whom to get in touch with to settle affairs. He detailed his motives for ending his life, citing the rupture of his family and the collapse of his finances, a five-year cliff dive from multimillionaire to a man who couldn't pay his condo fees. Mostly, though, he talked about a raft of ailments that pained and depressed him past all tolerance: starburst headaches and blurred vision, maddening craters in his short-term memory, and his helplessness getting around the towns he knew. Once a man so acute he aced his finals at Notre Dame with little study time, he found himself now having to dash down memos about what he was doing and when. Names, simple words, what he'd eaten for dinner — it was all washing out in one long wave.

No one had to tell him what those symptoms implied or what lay in store if he stuck around. Once a savage hitter on the best defense the game has ever seen, Duerson filled the punch list for chronic traumatic encephalopathy (CTE), the neuron-killing condition so rampant these days among middle-aged veterans of the National Football League. Andre Waters and Terry Long, both dead by their own hands; John Mackey and Ralph Wenzel, hopelessly brain-broke in their 50s. It was a bad way to die and a worse way to live, warehoused for decades in a fog, unable, finally, to know your own kids when they came to see you at the home.

Among the personal effects Duerson arranged that night in February was the master clue to the act he'd soon commit, Exhibit A in a life turned sideways: his 1987 NFL Man of the Year trophy. It was a testimonial to a former colossus, a player whose brilliance on the football field was a taste of much grander things to come. Future meat-processing pagnage and potential congressman, or successor to

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Gene Upshaw as director of the NFL Players Association – that Dave Duerson was all forward motion, the rarest amalgam of outsize smarts and inborn ambition. This version, though – the one slumped in bed with the .38 Special to his chest – this one had run into walls, head lowered, and he, not the walls, had buckled first.

Still, when someone turns a gun on himself, there are bound to be messy questions. Why, given the spate of concussions in the NFL season just past, would Duerson elect to keep silent about his suspected ailment at precisely the moment he should have spoken? Why would a man who knew as much about brain woes as anyone who's ever played the game, having served for six years and read thousands of case files as a trustee on the NFL's pension board, not have sought treatment and financial compensation from the very committee he sat on? And why, bizarrely, did he deny those very benefits to the men who needed them most, brain-dimmed veterans living in pain and squalor and seeking relief from the league?

Perhaps to stanch these questions, Duerson dispatched a blitz of texts in the last couple of hours of his life, some of them making an emphatic plea: Get my brain to the NFL's brain bank in Boston. The meaning of the texts seems plain enough: I'm sick and my mind's failing from all the helmet-to-helmet collisions in 11 brutal seasons in the NFL. Please see to it that my cortex is studied by doctors seeking treatments for brain trauma – and inquire no further about my reasons. It was a grandiose gesture, killing himself at 50 so that current and future players might be spared this horror, and was italicized by a second theatrical stroke: He shot himself through the heart, not the head, to preserve his brain for science.

But the dramatics of the act didn't sanctify him or absolve him of blame for the part he'd played in the suffering of other ex-players. If anything, Duerson's death has become a referendum on his, and his sport's, brutality, a prism through which to finally take a look at the cost of all those hits. If you're the kind of fan who keeps a mental lineup of ex-players headed for bad endings, Dave Duerson was the last name to make your list. Virtually from birth he'd been a special case, a gold-star guy who didn't bull through problems so much as soar above them. The youngest of four children born to Julia and Arthur Duerson Jr. in working-class Muncie, Indiana, he was as exceptional off the field as he was on it. A big, powerful kid with a nose for the ball and the long-stride speed to get there first, he dominated boys two and three years older in football from the time he hit sixth grade. (He excelled at baseball and basketball, as well.) Even then, though, his dreams were broader than jock stardom. Among friends he talked brashly about owning his own factories and running for the Senate someday. Duerson made the National Honor Society in high school, learned the trumpet and tuba by the age of 15, and toured overseas in an ambassador's band while earning 10 varsity letters.

With his pick of football factories like Texas and USC, Duerson chose South Bend for its glorious campus and network of corporate contacts. "From when I met him in seventh grade, he was positioning himself for a career after football," says Dave Adams, Duerson's teammate at Northside High and his roommate at Notre Dame. He interned at a law firm, then for Indiana Senator Richard Lugar.

"Sports were the springboard," says his ex-wife Alicia, who met him at a bowl game his freshman year. "He made so many plans for such a young age and had the brains to pull it all off. He had a photographic memory, which used to make me mad, because he'd barely study and get A's, where I'd be up a week of nights and be happy to get a B." A four-year starter at Notre Dame and a team captain, Duerson was as proud of his degree in economics as of making All-American, which he did twice.

Duerson was nothing if not complicated. He had, besides ambition and swagger to burn, a deep well of kindness and soul. You could see it in the way he honored Muncie, returning each summer to run a camp for poor kids in memory of a high school friend who'd drowned, and you could hear it later from the teens he sent to college after making it big with the Bears. "Everything he did was a teaching tool," says Michael Gorin, a family friend and retired teacher from Muncie whose son Brandon attended Duerson's JA3804

camp and went on to play nine years in the NFL. "He had the Super Bowl rings but kept harping on academics. My son says they talk about him at Harvard."

Harvard would come later, after Duerson got done playing and commuted to Cambridge for an executive program at the business school. Long before that, though, he got a brawler's education when he showed up at Bears training camp as a third-round pick. He should have gone higher in the '83 draft, but his talk about law school and political aspirations probably set him back a round or two. Buddy Ryan, the great, brutish coordinator of Chicago's 46 defense, loathed rookies, especially rookies with more on their mind than earholing Packers. "He knew I'd gone to Notre Dame and asked if I was one of those doctors or lawyers," Duerson said in an interview he gave last year for a book about Americans turning 50. "I said, 'Yes, sir.' He said, 'Well, you won't be here long, because I don't like smart niggers'" — a comment Ryan has denied making.

Dan Hampton, a Hall of Fame lineman on that absurdly dominant Bears defense, offers a different take. "Buddy didn't care if you were black, white, or green: He wanted smashmouth, and Duerson wouldn't nail guys. In practice, Buddy'd yell, 'That shit ain't cuttin' it! You dive on the ground again, I'm firing you!"

Duerson submitted to doing it Ryan's way and became a ferocious hitter. He mostly covered kicks his first two seasons and backed up Pro Bowl safety Todd Bell. Then, in '85, Bell held out for more money, and Ryan had no choice but to start Duerson. "I played through that whole season with [Buddy] telling me that he was rooting for me to screw up," Duerson said in a 2005 interview. "So I became an All-Pro myself." On that banzai unit, which jammed the line with 10 men, Duerson came screaming off the edge on blitzes. In 1986, his second season as a starter, he had seven sacks, a record for defensive backs that stood till 2005. He made the Pro Bowl four years running, a breakout star on a squad of loud assassins. Tellingly, it was Duerson who, with linebacker Otis Wilson, developed the unit's calling card. After an especially vicious shot, they'd stand over their victim, barking and baying like junkyard dogs.

Of course, football has a way of evening things up between predators and prey. In his 11-year run with the Bears, Giants (where he won another Super Bowl, in 1990), and Cardinals, Duerson suffered multiple minor concussions, though he was never knocked out cold. Emerging after games in a pair of dark glasses and wincing against the dusk, he'd complain of nausea and ringing headaches, says his ex-wife Alicia. "Dave would get concussed on the first or second series and play the whole way through, or get a dinger in the second half and be back at practice Wednesday morning," she says. "Dave had one speed, and that was full-out."

In the years to come, he'd have cause to rethink that, at least when it came to his kids. His middle son, Tregg, now a bank analyst in Chicago, was a highly regarded prep-school running back who'd go on to play defensive back at Notre Dame. One game in high school, Tregg was dazed from a tackle and wobbled off the field. Watching from the stands, Duerson ran down to the sideline and snatched Tregg's helmet so he couldn't return; at halftime he whisked him off to the hospital to be checked out. Tregg had a concussion. "Just to be on the safe side," says Alicia, "Dave wouldn't let him play for three games." As his playing days dwindled, Duerson weighed his options, beginning with politics. "Both the Republican and Democratic parties in Chicago tabbed him to run for office," says Harold Rice, one of Duerson's oldest friends and the man who accompanied Alicia and Tregg to Florida after Duerson's death. "Dave wanted to be a difference maker, but realized pretty quick that it wasn't worth the scrutiny."

Rice, who owned a McDonald's, urged him to enter his business instead. Duerson opened a franchise in Louisville, Kentucky, his first year out of football, then got an attractive offer from a McDonald's supplier: There was an ownership opportunity in a meat-processing plant an hour outside Chicago. Duerson bought a controlling stake and, with his contacts and charm, promptly doubled the plant's JA3805

revenue to more than \$60 million a year. He bought himself a huge house in Highland Park, just up the road from Michael Jordan's place, engraved his jersey number, NFL 22, on the driveway pillars, and spent a bundle on exotic cars, including a midnight-blue Mercedes SL 600 with the vanity plate DD22. By then he'd had four kids with Alicia, had local sports talk shows on both radio and television, and was jetting off to Cambridge, Massachusetts, for months at a time for the executive program there. "Dave loved it at Harvard, getting to network with CEOs and bounce ideas off presidents of foreign companies," says Alicia. "When he took us to Europe, it was first class all the way: stretch limos, four-star dining, and — his big dream — flying in the Concorde."

But friction eventually sparked between Duerson and his partner at the plant, who resented his comings and goings. In 2002, Duerson sold his interest to open his own processing plant nearby. It was the first big mistake in a life of shrewd decisions, and caught Duerson flat-footed, stunned by failure.

From the beginning, Duerson Foods had disaster written all over it. He shelled out millions to gut and double the factory's floor space, then borrowed heavily to buy state-of-the-art freezers from a company in the Netherlands. They were impressive to look at but so unsound that he had to postpone opening by six months. He fell behind on his schedule to supply Burger King and Olive Garden, and soon he was leveraged to the hilt. At his swank offices in Lincolnshire, Illinois, employees, some of them relatives, saw a change. His niece, Yvette Fuse, would call Rice in a panic to say that "Dave was berating people, acting mean." Duerson borrowed more, using his house as collateral, and sued the freezer maker. He won a \$34 million judgment, but the company filed for bankruptcy and never paid him a dime. By 2006, creditors were raining down lawsuits, and Duerson, broke and heartsick, shut the plant. He'd lost his mother to a heart attack and his house to the finance company, and his father was ailing with Alzheimer's (he died in 2009). "The pressure on him was phenomenal," said Rice. "It would've taken Superman not to break."

As it turned out, Duerson had broken, if briefly. In February 2005, he and Alicia drove to South Bend for a meeting of Notre Dame's board of trustees, of which he was a member. During a small-hours argument at their hotel, he threw her out the door of their room into the hallway wall. Alicia suffered cuts to her head and went to the ER with dizziness and pain. Duerson was charged with several misdemeanor counts and later pleaded guilty to domestic battery. In an interview, he called that night "a three-second snap," but it was played up big in the Chicago papers and forced his resignation from Notre Dame's board of trustees. Alicia, looking back now through the prism of his death, sees a clear demarcation in his conduct. The old Dave, she says, "would never do that; he never showed violence toward me. It was the changes," she says of his new hair-trigger temper, sudden downshifts in mood, and lack of impulse control – all signs of brain trauma.

His missteps, meanwhile, were beginning to throw shade on his fine reputation in the game – a reputation he'd carefully nursed since the day he entered the league. As a rookie in Chicago, Duerson had been chosen by his teammates to be the Bears' union representative. He was the son of a strong labor man at General Motors and "wanted to make things better for the guys," says Alicia.

For more than 60 years, the owners had run roughshod over the players, shackling stars to teams and imposing whatever terms they liked in collective negotiations. Duerson deftly held the Bears together through the bitter 1987 strike and beyond, and became a key adviser to, and close friend of, Gene Upshaw, the union's chief executive. "The two of them traveled together, even during the season, to talk to players about their rights," says Alicia. "Dave believed in the cause with all his heart and set himself to learning about labor laws so he could explain it clearly to the guys."

In 1992 and 1993, the players finally turned the tables in a pair of historic trials in federal court. Duerson was a featured plaintiff in one, and his tour de force performance on the witness stand helped fray the owners' resolve to keep on fighting. "He was so knowledgeable on the facts and spoke them so

beautifully that you could really feel the tide start to turn," says ESPN.com legal analyst Lester Munson, who covered the trial for Sports Illustrated.

The owners grudgingly cut a deal, awarding free agency and a broad slate of rights to players. Among the key gains was the creation of a board to hear the disability claims not only of active players but of retirees whose injuries prevented them from holding a job. The board was composed of six trustees (three each of management and union members, the latter being appointed by Upshaw), and the disability money, many hundreds of millions of dollars, was funded almost entirely by owners.

Right from its inception, though, an odd thing happened: In case after case before the board, former players were denied assistance or put through a maze of second opinions and paperwork. Men with bent spines and diced joints were told they could still hold a paying job and so were ineligible for aid. Then there were the veterans coming forward in their 40s and 50s with the brain scans of aging boxers who also had their claims voted down by the board. "They made it real clear that they'd fight me to the death, like they did with Mike Webster," says Brent Boyd, a Vikings guard in the '80s who suffers from clinical depression related to brain trauma. (Webster, the Hall of Fame center of the Steelers, was profoundly impaired by CTE and lived out of his truck at times before he died at 50.) "They were supposed to push for us, but were in the owners' pockets. You had to live in a wheelchair to collect."

In 2006, a particularly fraught time in the struggles between veterans and the players union, Upshaw decided to name his old friend Duerson to the pension board. This seemed a peculiar choice at best: Duerson had been out of the sport for a decade, was tarnished by the recent incident in South Bend, and ran a company that was coming apart. Any doubts about Duerson – and Upshaw's critics had plenty – were quickly ratified by his demeanor. The man who'd been so eloquent in federal court under the grilling of NFL lawyers was barging around town like a pit bull on crank, attacking former players at every turn. At a congressional hearing in 2007 to investigate the ex-players' charges, Duerson started a shoving match with Sam Huff and Bernie Parrish, two former greats speaking out for injured vets. He maligned Brent Boyd to a Senate committee, questioning whether his documented brain woes were actually caused by football. He took to talk radio to disparage Mike Ditka, saying his old coach, who'd raised money for vets, had never cared about his players' health. The worst of it, though, was his sliming of Brian DeMarco, a crippled veteran with several crushed vertebrae who'd gone public about his rejection by the union. Duerson tore into him on a call-in radio show, deriding him as a liar and an insurance fraud, then appeared on a Chicago TV program to ambush DeMarco in person.

His mad-dog behavior was very much in line with the way he voted on claims. Says Cy Smith, the lawyer who won a landmark lawsuit on behalf of Mike Webster's estate: "I get dozens of these files coming across my desk — stark, sad cases of guys really banged up — and the vast majority of these judgments are 6—0 against the players. That's a gross breach of practice by the board and a clear pattern of bias against paying." That Duerson was siding with management — and, apparently, Upshaw — is no surprise to his critics. Says Huff, the New York Giants Hall of Fame linebacker: "Dave wanted Gene's job when he finally stepped down, and was saying and doing whatever Gene wanted, or whatever he thought he wanted." Indeed, Duerson told people he'd been handpicked by Upshaw to succeed him as union chief, a position that paid nearly \$7 million a year and was essentially a lifetime appointment. When Upshaw died in 2008, Duerson didn't get the post (attorney DeMaurice Smith did), though he retained his seat on the board.

Whatever Duerson's motives for voting against veterans, they ran counter to a life spent helping others. At Duerson Foods, he'd paid the healthcare premiums for his factory-floor workers and footed the college tuition for kids from inner-city Chicago. That doesn't assuage the retired players he turned down, whose rancor isn't softened by his death. "He caused more suffering personally than all the other board members combined," says Boyd. Adds John Hogan, a lawyer who assists former players with their disability JA3807

claims: "He really could've changed the story for vets, and done it from the inside without saying mea culpa. He didn't have to indict the system. All he had to do was say, publicly, 'I'm sick, and I need help like these other guys.' "

The last years of his life, duerson knew he was in decline. He'd gotten divorced from Alicia in 2009 and fled to Florida in glum retreat, dropping out of sight for months on end. (He'd bought the condo, in the twin-tower Ocean One, in Sunny Isles Beach, as a winter house in 2000, but hadn't much used it until he moved in.) On his trips to Chicago to see his kids, he'd complain to Alicia about persistent headaches and frightening spells of blurred vision. "He thought at first he was getting old, but seemed more concerned as time went on," she says. His memory was shot, he wasn't sleeping much, and he had to ask her directions to get around Chicago – a town he'd known cold for 25 years. "He could hide the changes from friends and such, but he couldn't hide them from me. He'd say, 'Remember the time we did such and such?' as if to prove he wasn't fading, but he was."

He was a step above flat broke and trying to hide that, too. He hocked his wedding ring and Rolex watch, unloaded a newer Mercedes and his beloved Harley, and borrowed heavily against the equity in his apartment, though he'd put the place in trust for his four children. Even so, he couldn't make his child-support payments or keep up with his condo fees, and the stress and shame compounded his symptoms and began, it seemed, to derange him.

Says Ron Ben-David, who took over as building manager at the Ocean One towers in 2008: "I called Dave down and asked him politely why he hadn't paid his dues in almost a year. He told me someone had broken into his closet and stolen three paintings he'd bought in Cuba, and unless we reimbursed him the \$7,000, he wasn't going to pay the arrears." But Duerson hadn't phoned the cops about his loss or filed an insurance claim, and ultimately paid his back-maintenance fees via wire transfer. A year later, his checks stopped coming again, and again Ben-David called him down. "He said, 'Well, someone stole my paintings. Aren't you going to reimburse me?' And this time they were worth \$30,000."

"He was definitely getting worse. I could hear it over the phone," says Alicia. "He was trying to reinvent who he was at 50, and that's hard even when you're thinking straight." Duerson talked a lot about having "irons in the fire" – some deals in the works with Costco and the USDA – but nothing ever seemed to pan out. When he filed for bankruptcy in Florida last year, he showed annual expenditures of \$74,000, an income of less than \$34,000, and a consulting business whose only assets were the furniture and equipment in his study. His one frail hope, a Hail Mary, was to get hired as a coach in the NFL. Last fall he phoned Steve Zucker, his former agent, and asked him to make some calls on his behalf. At the time, he had several ex-teammates running teams – Jeff Fisher, then with the Titans, Mike Singletary, then with the 49ers, and Leslie Frazier, who'd taken over in Minnesota – all three also proud alumni of that great Bears defense of the '80s. "His plan was to get a position-coach thing or a job in someone's front office," says Zucker, once a Chicago superagent who is now in his 70s and mostly retired. "I talked to him all the time and had no idea. He sounded so positive on the phone."

With the exception of Alicia and a couple of his old cronies, Duerson told no one how grim things had gotten or how badly his symptoms had unhinged him. He holed up in Florida, where he avoided his neighbors. Beyond the occasional visit from one of his kids, the only break in the deepening gloom was a last-chance love affair. He'd met Antoinette Sykes in May 2010 at a business conference in Las Vegas, where he gave a talk to aspiring entrepreneurs about growing and selling a million-dollar company. By summer, he and Sykes, who owns her own PR and marketing firm in Washington, D.C., were speaking or texting 10 times a day and flying to each other's homes for weeklong stays. In the fall, he proudly showed her off to building manager Ben-David, calling her his "angel" and fiancée. They were scheduled to be married in April 2011, when his daughter, who would be on spring recess, could attend.

"What we shared was so sacred and joyful," Sykes said over the phone from D.C. "I knew he had headaches and – and a lump on his skull that he was worried about, but what I'm reading in the papers now about his brain, it's thrown me for such a loop. Maybe he wanted to shield me, but he seemed so excited about spending the rest of our lives together. On our last night, Valentine's, he joked that I owed him 29 more because we'd committed to 30 years of wedded bliss. And then I flew home to pack my things to move down there..." She breaks off, convulsing.

On February 17, Sykes woke up in Washington to a text from Duerson. It began, "My dear Angel, I love you so much and I'm sorry for my past, but I think this knot on my head is the real deal." Sykes called him, heard nothing back, and became frantic as the morning passed. Sometime after two that afternoon, she called Ben-David and asked him to knock on Duerson's door. When no one answered, she faxed him her permission to use a spare key. "I got the door open, but there was a chair wedged against it. That's when I called 911," he says. Paramedics and cops arrived and pushed their way in. "I heard them in the bedroom, yelling 'Sir! Sir! Is everything all right?' Then they asked me to leave," says Ben-David. Duerson was found shortly after 3 pm. He had shot himself about 12 hours earlier. Apart from the large patch of blood beneath him, the place was immaculate, said Miami-Dade police officers. Veteran detectives, they said they'd never seen a suicide planned and executed so meticulously.

In the months after his death, Duerson has become a wedge for practically anyone with a connection to the sport. The media has mostly lined up with 'Time' magazine, which called him "football's first martyr." Ex-players have sourly mocked his sanctification, denying him any credit for calling attention to CTE in death when he could have worked for justice while alive. Even his Bears teammates are badly split: Some are saddened and shocked by his death, while others deem him selfish and arrogant — "political to the end," groused a former lineman. The dissonance was put best by his son Tregg, now 25. "I just wish he'd played baseball," he told the New York Times five days after Duerson died. But, he added, sobbing, that his father "was looking for an answer and was hoping to be part of an answer."

At some point, it's hoped, Duerson's motives will matter less than the long-haul impact of his passing. A tremor has gone through the league, deep and wide; players are talking openly about football and brain cells and fretting over their own neural health. "Is it something that I think about? Yeah, absolutely," Baltimore Ravens center Matt Birk told the Times. He's one of more than a hundred current and former players who've signed over their brains for postmortem study at Boston University. You'd expect forward thinking from a Harvard grad like Birk, rated the sixth-smartest man in sports by Sporting News last year. But the message is getting across to less cerebral types, too. Jim McMahon, the ex-passer and party monster who loved to celebrate touchdowns with ringing head butts, is battling serious memory problems and has also agreed to send his brain to Boston. "What the fuck do I need it for when I'm dead?" he says. That gesture, if not the sentiment, will be part of the answer to the questions Duerson lived and died to raise.

EXHIBIT 75

Blogs » Dave Zirin » Are Head Injuries the Bridge Between the NFL Playing Field and Domestic Violence?



Are Head Injuries the Bridge Between the NFL Playing Field and Domestic Violence?

Dave Zirin on September 21, 2014 - 7:13 PM ET



NFL Commissioner Roger Goodell (AP Photo/Seth Wenig)

There is an unspoken question lurking behind the NFL domestic violence cover-up saga that has emerged over the last month. It is whether the brutality of the game, particularly head injuries, plays a role in the prevalence of players committing acts of violence against women. The NFL has a vested interest in not having this discussion. On head injuries, as the title of the award-winning book said so clearly, it remains "a league of denial." If, in the name of public relations, the owners won't have a discussion about the connection between their sport and horrific post-concussive syndromes like ALS and early-onset dementia, are they really going to talk about links between head injuries and domestic violence? The sports media are largely in denial about this topic as well, as there was not one question in Roger Goodell's instantly infamous Friday press conference about whether the league would investigate whether brain injuries could be the bridge between the violence at work and the violence at home.

Yet many domestic violence advocates are also—understandably—not thrilled with this line of discussion. Partner abuse occurs in all walks of life, all professions and among all income groups, and post-concussive syndromes are almost always not a part of those stories. Additionally, to blame it on concussions seems to be excusing domestic violence and denying the fact that NFL players have agency and choice before becoming abusers. This resistance is very understandable. But attempting to explore and explain the shockingly high rates of domestic violence in the NFL is not the same as excusing it.

So is there a connection? As my friend Ruth, who is a DV counselor, says, "When it comes to

domestic violence, it is extremely difficult to generalize across the board, in the NFL or otherwise." In other words, every case is distinct, reflecting the interpersonal relationships of the parties involved. But there are factors that appear to show themselves in the football cases with alarming regularity. Some of these factors are high rates of stress, a culture of entitlement for sports stars that predates their life in the NFL, and an inability to turn off the violence of the game once the pads are off. This is when we see the most toxic part of the sport's hyper-masculinist culture poison the relationships between the men who play the game —as well as the men who own teams—and the women in their lives. But among many players, this question of the role of head injuries still lingers in the background.

Dan Diamond over at *Forbes* is one of the few journalists I have seen explore these links in detail. In one piece, he cites a "disturbing new report" that shows "3 in 10 NFL players suffer from at least moderate brain disease." Diamond then details many examples of former players who were found in their autopsies to have the repetitive post-concussive syndromes known as CTE, and were also arrested at some point or another for domestic violence. He writes:

The key issue is whether suffering *repeated head trauma* lowers a person's self-control. And while many pro football players haven't been diagnosed with concussions in the NFL, nearly all of them have been playing football since they were young and suffered repetitive, frequent blows that can add up over time. And researchers know that those concussions can change a person. Even a pillar of the community.

This connects anecdotally with much of my own research. Over the last two months, I have spoken with three different women whose husbands are or were NFL players. All three are domestic violence survivors. In one case, the marriage was mended and endures to this day. In one case, it ended in divorce. In one case it ended with the suicide of the player in question. Yet that is where the differences ended. The similarities were stunning. In all three cases, the violence was precipitated either by migraine headaches or self-medicating—drugs or alcohol—to manage migraines. In all three cases, the survivors spoke about their NFL husbands becoming disoriented or light-sensitive, easily frustrated and quick to anger in ways that did not exist earlier in the relationship. In all three cases, they spoke about bizarre looks on their husbands' faces when they committed the abuse, from a chillingly peaceful calm to quizzical smiles. Whatever the look, they spoke of being in the presence of someone they "did not recognize."

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I also spoke with Matt Chaney, a former college football player and author of the book *Spiral of Denial: Muscle Doping in American Football*, about whether he believed there was a causal link between concussions and domestic violencw. He e-mailed me back the following. "I can't speak as medical authority on any link but as a journalist and academic who's read and filed tens of thousand documents on football hazards from violence to drugs, and one who's interviewed a thousand people, along with being a former college player who has knowledge of countless athletes and their relationships, I believe football brain injuries lead many players to violence they wouldn't otherwise have committed, ranging from domestic cases to random acts.... I think brain injuries, after studying the topic as we all have in recent years, now explains much about the perplexing cases of violence and other irrational behavior among football players I've known. And while I thought I abhorred street fighting, before college football, I found myself nearly involved with or nearly instigating such trouble on more than one occasion while I was in full-contact activity, fall and spring practices, banging my head. If I didn't have headache after a college contact session, I didn't think I'd done anything."

This question, of course, has profound implications well beyond the sport. It is about the choice families make whether to let their children play tackle football. It is about the health and safety of women in relationships with NFL players, and whether recognizing warning signs of CTE can create opportunities for intervention before abuse takes place. It is about the degree $\frac{1}{1438}$

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to which the league's very violence bears some complicity in their abuse. This is a difficult question, one Roger Goodell is loathe to discuss. That is exactly why we need to keep asking it.

EXHIBIT 76

THE LEGAL EXAMINER

10 06 2014 Headline: HBO Real Sports to Examine Link Between NFL Concussions and Domestic Violence 2 weeks ago Search

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Will NFL & NFLPA Admit Concussion Link to Domestic Violence?

Posted by Brett Emison September 16, 2014 8:32 AM

5 comments

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By now, most of America has seen (or at least heard about) the horrific video show NFL running back Ray Rice knocking out his fiancee in an elevator and then dragging her out into a casino hotel. You've also heard about problems with NFL running back Adrian Peterson or defensive end Greg Hardy or defensive end Ray McDonald. Most of America has also heard about the issue of concussions plaguing current and former NFL players. Most - if not all - of the media have been treating these issues as separate "crises" for the NFL and NFLPA. But science and medicine suggest we should be looking at these issues as symptoms of the same problem.

> Medical science has told us for years that brain injury is linked to violent acts. In 2013, the Toronto Sun reported that athletes who experienced repeated head injuries have an increased risk of becoming angry and violent. 73% of the young men studied were described as "explosive"; 64% were described as "out of control"; and 68% were described as physically violent.

An 8-year study published by the University of Michigan School of Public Health in the journal Pediatrics "does support some of the sports research that's been going on with concussions." Researchers noted that long-term effects of head trauma can include changes in cognition, language, emotion, irritability, impulsiveness, and violence.

"Head injuries range along a continuum from athletic concussions to traumatic brain injury suffered in war or a result of an accident. This study looks at head injuries from a broad perspective and confirms previous findings about the connection between violence and head injuries."

- Lead author, Sarah Stoddard, Ph.D, via PsychCentral

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The study found that violent effects could be seen quickly following a head injury.

Researchers studied the timing between a head injury and violent behavior and found that an injury reported in year seven of the study predicted violent behavior in year eight.

"We found that the link between a head injury and later violence was stronger when a head injury was more recent, even after controlling for other factors including previous violent behavior," Stoddard said.

- Rick Nauert, Ph. D. at PsychCentral

According to the group, synapse, people suffering head trauma may develop behaviors leading to domestic violence.

We all tend to let our hair down with family, as opposed to strangers or acquaintances. Of course, after a brain injury a person's interpretation of letting hair down may be well beyond what most would consider acceptable, particularly if their self-awareness has been affected. They may justify their violence by saying that others provoked them, not realizing that the brain injury has increased their sensitivity to stress and decreased their ability to handle it.

The frontal lobe is often damaged in brain injury. This area of the brain is involved in reasoning, problem solving and controlling our more basic instincts such as anger. An individual who has sustained a brain injury has often lost these skills and therefore may have trouble controlling anger and violent outbursts. In many cases brain injured individuals often lose some of the social judgment capabilities and are not effectively able to reason out the appropriateness of either their own behavior or the behavior they expect from others.

- synapse, Domestic Violence and Brain Injury



A 2005 study noted that aggressive behavior after a concussion or other traumatic brain injury includes explosive behavior that can be set off by minimal provocation and occur without warning. A number of studies have found frontal and prefrontal injuries or other abnormalities in people prone to impulsive aggression and violence. The frontal lobe and prefrontal network generally control impulse and behavioral reactions to provocation. Uninjured people are able to control negative feelings voluntarily and can process restraint-producing cues from their

environment, including facial and vocal signs of anger or fear. However, when frontal and prefrontal areas of the brain are injured, victims are less able to control their emotions and impulses. They are also more prone anger, aggression, and violence.

For More Information About NFLPA Concussion Lawsuits Click Here

Why have we not seen <u>anv</u> discussion of the link between concussions and other head trauma and domestic violence in the NFL? Just last Friday, the NFL dumped piles of data showing the severe risk its players at at for traumatic brain injury. According to the NFL data, nearly 30% of players will suffer brain injury significant enough to result in moderate-to-severe dementia. Twice the rate of the regular population at age 71.

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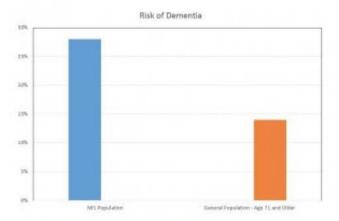
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Greg Hardy - found guilty of domestic violence in July 2014 - suffered a concussion during the 2010 NFL season. The other players in the news have not had a concussion documented on an injury report, but each of them is likely to have suffered numerous head traumas in their grinding NFL careers. Ray Rice even bragged that new NFL rules prohibiting running backs from using the crown of their helmet to contact defenders outside the tackle box would not change his running style.

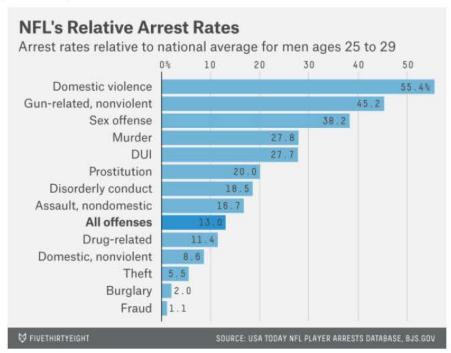
"I don't like it," Rice told the Ravens' official web site. "I'm just telling you right now, there's not going to be a guy that's going to be able to get a free lick on me and think it's all right. I will defend my case, and I will defend myself as a runner."

Rice and others contend that it's impossible for a back to protect himself without dipping his head and making contact.

"If I'm in the open field and you're coming at me and I'm coming at you, and I lower my shoulder and I get flagged, I'll appeal it," Rice said. You're going to protect yourself as a runner. Not one running back, you ask anyone in the league, not one is going to change their game."

- Kareem Copeland, NFL.com

It just makes sense that when the NFL generates a higher-than-normal level of brain injury, it generates a higher-than-normal level of domestic violence.



Since 2000, there have been 83 domestic violence arrests of NFL players, making this by far the

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NFL's worst category with a relative arrest rate of 55.4%. As Benjamin Morris at FiveThirtyEight, points out, this is "extremely high relative to expectations."

That 55.4 percent is more than four times worse than the league's arrest rate for all offenses (13 percent), and domestic violence accounts for 48 percent of arrests for violent crimes among NFL players, compared to our estimated 21 percent nationally.

Moreover, relative to the income level (top 1 percent) and poverty rate (0 percent) of NFL players, the domestic violence arrest rate is downright extraordinary.

- Benjamin Morris at FiveThirtyEight

No one is defending the actions of these players off the field. I'm certainly not doing that here. A brain injury can never be an excuse for domestic violence. But why hasn't the league and why hasn't the Players Association made the link between the level of brain injury and the level of domestic violence when the science is so strong and so straightforward.

The NFL and the NFLPA have a concussion and brain injury problem. The league and the Players Association have a domestic violence problem. But the science suggests they are not <u>separate</u> problems at all.

When the NFL has already acknowledged significant brain injury resulting in dementia in almost 30% of its players, why isn't the league and - more importantly - why isn't the NFLPA doing something more to protect these players and their families?

Read More:

- Domestic Violence and Brain Injury [synopse]
- Breaking the Silence: Violence as a Cause and a Consequence of Traumatic Brain Injury [Jean Langlois at Brain Injury Professional magazine via brainline.org]
- Ray Rice: New helmet rule won't change my game [Kareem Copeland at NFL.com]
- The Rate of Domestic Violence Arrests Among NFL Players [Benjamin Morris at FiveThirtyEight]
- Violence and Aggression The Dana Guide [Antonio Damasio at The Dana Foundation]
- Study: 30% of Former NFL Players Will Develop Dementia
- NFL Star Suffering Memory Loss After Concussion Injuries
- More Players Join Concussion Lawsuits Against NFLPA

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EXHIBIT 77

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Short Communications

Profile of Self-Reported Problems with Executive Functioning in College and Professional Football Players

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Abstract

Repetitive mild traumatic brain injury (mTBI), such as that experienced by contact-sport athletes, has been associated with the development of chronic traumatic encephalopathy (CTE). Executive dysfunction is believed to be among the earliest symptoms of CTE, with these symptoms presenting in the fourth or fifth decade of life. The present study used a well-validated self-report measure to study executive functioning in football players, compared to healthy adults. Sixty-four college and professional football players were administered the Behavior Rating Inventory of Executive Function, adult version (BRIEF-A) to evaluate nine areas of executive functioning. Scores on the BRIEF-A were compared to published age-corrected normative scores for healthy adults Relative to healthy adults, the football players indicated significantly more problems overall and on seven of the nine clinical scales, including Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, and Task Monitor. These symptoms were greater in athletes 40 and older, relative to younger players. In sum, football players reported more-frequent problems with executive functioning and these symptoms may develop or worsen in the fifth decade of life. The findings are in accord with a growing body of evidence that participation in football is associated with the development of cognitive changes and dementia as observed in CTE.

Key words: chronic traumatic encephalopathy; executive function; football; traumatic brain injury

Introduction

RAUMATIC BRAIN INJURY (TBI) is a significant public health problem. It is estimated that approximately 1.7 million TBIs occur in the United States annually, resulting in emergency department visits, hospitalization, or death, with direct and indirect costs totaling approximately \$76.5 billion a year. ¹⁻³ Moderate to severe TBI (sTBI) is associated with a wide range of long-term cognitive deficits. ⁴ Though early research focused on the effects of moderate to sTBI, attention has increasingly turned to the long-term consequences of repetitive mild TBI (mTBI), such as that experienced by contact-sport athletes. It has been estimated that 1.6–3.8 million sport-related mTBIs occur annually, ^{5,6} with the greatest number occurring in football. ^{7,8} With over 60 million youth and adolescents participating in organized sports each year, a number that increased by 16 million from 1997 to 2008, sport-related TBI is an important and growing public health concern. ^{9,10}

The recent deaths of several high-profile athletes have resulted in significant public and scientific interest in the long-term effects of mTBI and chronic traumatic encephalopathy (CTE), a progressive neurodegenerative disease linked to repetitive brain trauma. Helmet sensor data indicate that football players can experience more than 1000 hits to the head over the course of a season. 11 This repetitive exposure has been associated with the development of CTE and changes in cognition, mood, and behavior that begin in the fourth to fifth decade of life and eventually progress to dementia. 12–17 Epidemiological studies indicate that professional football players are at least four times more likely to receive a diagnosis of memory impairment or dementia and have at least a three times greater risk of dying from a neurodegenerative disease, compared to the general population. 17,18 To date, all cases of neuropathologically confirmed CTE have had a history of repetitive brain trauma; therefore, repetitive brain trauma appears necessary for the development of the disease. 15,19 However, brain trauma alone is insufficient to lead to

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neurodegeneration in all individuals (i.e., not everyone with repetitive TBI gets CTE). 15

To date, relatively few studies have examined cognitive functioning in football players during life. Amen and colleagues found that active and retired football players scored in the bottom 50th percentile on three indices (attention/mental control, memory, and reasoning) of a computerized assessment of neuropsychological status. Former university hockey and football players who sustained concussions have been found to perform worse on measures of memory and attention/executive function decades after their last concussion. These studies indicate that executive functioning is impaired in former contact-sport athletes many years after the athlete's last exposure to brain trauma.

The long-term effects of repetitive brain trauma on cognition have yet to be examined using a standardized self-report measure of executive function. The Behavior Rating Inventory of Executive Function, adult version (BRIEF-A) was chosen for this study because of its use in clinical neuropsychological assessments and wellestablished normative data. Additionally, reports indicate that the BRIEF-A is sensitive to early executive deficits, before they might typically present on objective measures of cognitive function.²² The aim of this study was to examine executive function in current and retired college and professional football players, a group at high risk of exposure to repetitive mTBI, using the BRIEF-A. We hypothesized that these football players would report more-frequent problems with executive functioning than healthy, same-age control participants. Because CTE symptoms typically present in the fourth or fifth decade of life, we hypothesized that football players over 40 years of age would report more-frequent problems than younger athletes.

Methods

This project was part of an ongoing longitudinal study examining cognitive function in current and former athletes. Inclusion criteria include being at least 18 years old and having a history of participation in organized sports at any level of competition. Recruitment methods include the following: (1) inclusion of the study on the Center's website and the website of the Sports Legacy Institute; (2) lectures and presentation at a variety of events for athletes at all levels of play; and (3) word of mouth. All participants

are self-referred. This larger project (the Longitudinal Examination to Gather Evidence of Neurodegenerative Disease; LEGEND), requires completion of yearly telephone interviews and online questionnaires. Participants are sent an e-mail link to complete the online questionnaires, which include self-report measures of cognition, mood, and performance on activities of daily living. Demographic characteristics, athletic experience, and concussion history, as well as participant and family medical and psychiatric history, are also obtained. Subsequent to completion of the online questionnaires, participants are contacted by phone to complete the telephone interview. The present study included all college and professional football players in the LEGEND study at the time of data analysis.

Participants

Participants included 64 male current and retired football players, ranging from 25 to 81 years of age (mean, 47.0; standard deviation, 13.6). All LEGEND participants with a history of participation in college or professional football were selected for analysis. The football players were grouped by highest level achieved and age greater than or equal to 40. Demographic and athletic characteristics of the groups are listed in Table 1. All participants provided informed consent for the protocol approved by the Boston University Medical Center Institutional Review Board (Boston, MA).

Measures and procedures

Participants completed an online version of the BRIEF-A, a 75-item self-report measure of executive functioning in everyday activities over the past 30 days. Participants were instructed to answer the following question for each statement: "During the past month, how often has each of the following behaviors been a problem?" Responses use a three-point scale, scored as follows: never=1; sometimes=2; and often=3. Higher scores indicate worse executive function. These responses yield an overall composite score (Global Executive Composite; GEC), two index scores [Behavioral Regulation Index (BRI) and Metacognition Index (MI)], and the following nine clinical scales: Inhibit; Shift; Emotional Control; Self-Monitor; Initiate; Working Memory; Plan/Organize; Task Monitor; and Organization of Materials. Each clinical scale includes 6–10 items. The BRI index is composed of the Inhibit, Shift, Emotional Control, and Self-Monitor

TABLE 1. DEMOGRAPHIC CHARACTERISTICS

Characteristic	$AP \\ (n = 64)$	<i>CF</i> (n = 35)	<i>PF</i> (n = 29)	<40 (n=22)	≥ 40 $(n=42)$
Mean age, years (SD)	47.0 (13.6)	45.9 (14.1)	48.3 (13.0)	33.0 (3.9) [†]	54.3 (10.8)
Age range	25–81	25–78	27–81	25–39	41-81
Education (terminal degree)					
High school/GED, %	1.6	0	3.4	0	2.4
Associates/certification, %	1.6	2.9	0	4.5	0
Bachelor's degree, %	65.6	57.1	75.9	68.2	64.3
Master's or doctoral degree, %	31.3	40	20.7	27.3	33.3
Athletic history					
Total years of football (SD)	13.0 (5.1)	9.5 (2.7)	17.2 (3.9)*	11.8 (4.3)	13.6 (5.4)
Years played in college (SD)	3.7 (1.0)	3.3 (1.3)	4.2 (.51)*	3.7 (1.1)	3.9 (0.85)
Years played professionally (SD)	3.0 (4.1)	N/A	6.4 (3.6)	2.2 (3.8)	3.6 (4.2)
Professional: college	N/A	N/A	N/A	8:14	21:21
Number of concussions (SD)	350.8 (2516.0)	24.9 (23.8)	758.1 (3771.7)	22.8 (223.2)	526.7 (3117.8

< 40 indicates players 39 years of age and younger, whereas ≥ 40 indicates players 40 or more years of age.

^{*}Significant differences between CF and PF (alpha=0.05).

[†]Significant differences between <40 and ≥40 (p<0.05).

AP, all players; CF, college players; PF, professional players; SD, standard deviation; GED, General Educational Development.

subscales, and the MI index is composed of the Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials subscales.

Concussion history was obtained during a phone interview. Participants were provided the following definition of concussion:

"Some people have the misconception that concussions only happen when you black out after a hit to the head or when the symptoms last for a while. But, in reality, a concussion has occurred anytime you have had a blow to the head that caused you to have symptoms for any amount of time. These include: blurred or double vision, seeing stars, sensitivity to light or noise, headache, dizziness or balance problems, nausea, vomiting, trouble sleeping, fatigue, confusion, difficulty remembering, difficulty concentrating, or loss of consciousness. Whenever anyone gets a ding or their bell rung, that too is a concussion"

Based on this definition, participants were asked to state approximately how many total concussions they have had during their life.

Statistical analysis

Scores on the BRIEF-A were converted to age-appropriate T scores based on published normative data, which include 1050 participants selected to proportionally represent the U.S. population in regard to sex, race/ethnicity, education, and geographic region.²³ Elite football players may differ from this normative population in several ways, including exposure to repetitive brain trauma, physical stature (height and weight), educational attainment (generally higher), health (alcohol use, heart disease, arthritis, chronic pain, orthopedic issues, number of surgeries, depression, dementia, and use of medications), and health-related behaviors (increased alcohol use, decreased smoking, and illicit drug use).²⁴ For comparison of mean scores with normative data, one-sample t-tests were performed. For between-group comparisons, t-tests for two independent samples were performed. When indicated by Levene's test for equality of variances, degrees of freedom were adjusted to account for unequal variances. Because there were cases with zero counts in some cells, rates of clinically elevated scores (i.e., percent of individuals with a T score ≥ 65) were compared to additional normative data using Fisher's exact test. For the overall composite score (GEC) and index scores (BRI and MI), an alpha level of 0.05 was adopted. To control for type I errors, analyses of the nine clinical scales were conservatively adjusted for multiple comparisons using Bonferroni's correction (0.05/ 9 = 0.006). Analyses of the individual clinical scales were performed when significant group effects were observed on the overall composite score or one of the two index scores.

Results

Comparison between college and professional football players

Effects of competition level (i.e., professional vs. college) on the overall composite score and the two index scores were examined by independent sample t-tests. Scores on the GEC were similar between groups (t(44.2) = 2.0; p = 0.06). Professional and college football players indicated similar functioning on the BRI index (t(49.3) = 1.9; p = 0.06), but the professional athletes reported morefrequent executive functioning problems on the MI index (t(42.7) = 2.4; p < 0.05). Analyses of clinical scales revealed similar ratings between groups at each of the nine scales (all p values > 0.006). Given the similarity between groups, data from college and professional football players were combined for subsequent analyses.

Comparison between football players and normative data for healthy adults

Effects of participation in football were examined by one-sample t-tests comparing age-adjusted T scores with the known population mean of 50. Significant group differences were observed on GEC (t(63) = 5.4; p < 0.05), MI (t(63) = 5.3; p < 0.05), and BRI (t(63) = 5.2; p < 0.05). Analyses of the clinical scales indicated significant group effects on seven of the nine scales: Inhibit (t(63) = 5.8; p < 0.006); Shift (t(63) = 4.4; p < 0.006); Emotional Control (t(63) = 4.9; p < 0.006); Initiate (t(63) = 4.6; p < 0.006); Working Memory (t(63) = 6.6; p < 0.006); Plan/Organize (t(63) = 3.9; p < 0.006); and Task Monitor (t(63) = 4.8; p < 0.006). Differences between groups on Organization of Materials reached the corrected alpha level of 0.006, but was not below this threshold (t(63) = 2.8; p = 0.006), and groups were similar on Self-Monitor (t(63) = 1.4; t = 0.16). Across all scales, the football players indicated worse functioning than the normative sample.

Rates of clinically elevated scores (i.e., T scores \geq 65) between groups were examined by Fisher's exact test. Significant group differences emerged on GEC ($x^2(1, n=90)=9.1$; p<0.05), MI ($x^2(1, n=90)=13.3$; p<0.05), and BRI ($x^2(1, n=90)=8.5$; p=0.05). Analyses of the clinical scales indicated significant group effects on five of the nine scales: Inhibit ($x^2(1, n=90)=8.5$; p<0.006); Shift ($x^2(1, n=90)=7.9$; p<0.006); Initiate ($x^2(1, n=90)=9.1$; p<0.006); Working Memory ($x^2(1, n=90)=13.3$; p<0.006); and Plan/Organize ($x^2(1, n=90)=11.1, p<0.006$). The rate of clinically elevated scores was similar between groups on the remaining four scales: Emotional Control ($x^2(1, n=90)=5.9$; p=0.02); Self-Monitor ($x^2(1, n=90)=5.6$; p=0.02); Task Monitor ($x^2(1, n=90)=4.5$; p=0.05); and Organization of Materials ($x^2(1, n=90)=2.0$; p=0.27). Across all scales, the football players had higher rates of clinically elevated scores than the normative sample.

Comparison between younger and older football players

Effects of age group (i.e., <40 vs. \ge 40 years) on the overall composite score and the two index scores were examined by independent sample *t*-tests. Older athletes indicated more-frequent problems overall (t(62) = 2.7; p < 0.05), on the BRI (t(56.0) = 3.3; p = 0.05); and on the MI indices (t(62) = 2.1; p < 0.05), when compared to younger athletes. Analyses of clinical scales revealed group differences on two of the nine scales. Older football players indicated experiencing more problems on the Emotional Control (t(62) = 2.9; p < 0.006) and Initiate (t(55.8) = 3.2; p < 0.006) clinical scales. Scores on the remaining scales were similar between groups, including Inhibit (t(57.7) = 1.8; p = 0.08), Shift (t(62) = 2.5; p = 0.01), Self-Monitor (t(62) = 2.7; p = 0.01), Working Memory (t(62) = 1.4; t = 0.16), Plan/Organize (t(62) = 1.9; t = 0.07), Task Monitor (t(62) = 2.5; t = 0.02), and Organization of Materials (t(62) = 1.5; t = 0.14; see Table 3).

Correlations between BRIEF-A and athletic history

Correlations between BRIEF-A scores, self-reported concussions, and years playing football were determined by Pearson's correlation coefficients for all participants, separately for level of play and age groups. The number of self-reported concussions was log-transformed because of the non-normal distribution of these data. Overall, 56 of the 64 participants (87.5%) reported experiencing 55 or fewer concussions. For the remaining 8 participants, 6 reported experiencing between 100 and 140 concussions, 1

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Table 2. Comparison of Age-Adjusted T Scores between Football Players (College and Higher) and Normative Data for Healthy Adults on the BRIEF-A

	Football players ^a		Football ^a vs. healthy adults ^b		
	Mean (SD)	Percent of T scores ≥ 65	T-score p value	Cohen's d	T scores ≥65 p value
Index scores					
BRI	58.2 (12.8)	26.6	0.000*	0.81	0.004*
MI	59.4 (14.2)	37.5	0.000*	0.91	0.000*
GEC	58.9 (13.2)	28.1	*000.0	0.87	0.002*
Clinical scales					
Inhibit	58.4 (11.5)	26.6	0.000*	0.85	0.004*
Shift	56.3 (11.4)	25.0	0.000*	0.63	0.005*
Emotional Control	58.0 (13.0)	26.6	0.000*	0.79	0.015
Self-Monitor	52.3 (13.0)	18.8	0.159	0.23	0.018
Initiate	58.1 (14.1)	28.1	0.000*	0.79	0.002*
Working Memory	62.4 (15.0)	37.5	0.000*	1.20	0.000*
Plan/Organize	56.9 (14.1)	32.8	0.000*	0.67	0.001*
Task Monitor	57.6 (12.6)	28.1	0.000*	0.75	0.035
Organization of Material	54.3 (11.9)	14.1	0.006	0.43	0.162

Scores from football players were compared to age-adjusted normative data published in the BRIEF-A manual.

BRI, Behavioral Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite; SD, standard deviation.

reported experiencing approximately 350 concussions, and 1 reported experiencing approximately 20,000 concussions. These analyses were performed to determine if total years of play and/or number of concussions contributed to the between-group findings. In the overall sample, total number of years played correlated with Working Memory (r=0.29; p<0.05), and number of self-reported concussions correlated with Emotional Control (r=0.26; p<0.05) and Initiate (r=0.32; p<0.05). In the younger than 40 group,

Table 3. Comparison Between Age-Adjusted T Scores on BRIEF-A between Players Younger and Older Than 40 Years

	Football players less than 40 years of age (n=22)	Football players 40 and older (n=42)	p value
Index scores ^a			
BRI*	52.0 (9.4)	61.5 (13.2)	0.002
MI*	54.5 (13.9)	62.0 (13.8)	0.043
GEC*	53.1 (10.7)	62.0 (13.5)	0.010
Clinical scales ^b			
Inhibit	55.3 (8.5)	60.1 (12.5)	0.075
Shift	51.5 (9.9)	58.8 (11.4)	0.014
Emotional Control*	51.9 (9.9)	61.2 (13.4)	0.005
Self-Monitor	46.5 (10.1)	55.4 (13.4)	0.008
Initiate*	51.4 (10.5)	61.6 (14.6)	0.002
Working Memory	58.7 (12.0)	64.3 (16.2)	0.158
Plan/Organize	52.4 (11.8)	59.2 (14.7)	0.067
Task Monitor	52.4 (10.9)	60.4 (12.7)	0.015
Organization of Material	51.2 (10.3)	55.9 (12.5)	0.138

All means and standard deviations are reported.

BRI, Behavioral Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite.

number of self-reported concussions correlated with Inhibit (r=0.54; p<0.05). In the older than 40 group, total number of years played correlated with Working Memory (r=0.37; p<0.05). No other correlations were significant.

Discussion

In this study, we examined a self-report measure of executive function in current and retired college and professional football players, a group with high exposure to repetitive brain trauma. Overall, we found that football players reported more-frequent problems with executive function in everyday activities, when compared to published normative data for healthy individuals of the same age and representative of the U.S. population in regard to sex, race/ethnicity, education, and geographic region. Scores were elevated overall, as well as on specific indices of the ability to control behavior and emotional responses and the ability to methodically solve problems through planning, organization, and sustaining effort. Despite higher scores overall, considerable variability was observed across participants, indicating that not all elite football players experience executive dysfunction.

It should be highlighted that the football players reported a normal frequency of problems on monitoring the effects of their behavior on others. Taken together, this profile suggests that football players may be aware of any effects they may have on others, but are unable to change their behavior because of weaknesses in thinking flexibly and inhibition. It is plausible that this may contribute to depression observed in former athletes with CTE. ¹⁵ It should be emphasized that executive dysfunction has several etiologies, and not all football players with these symptoms will develop CTE.

Consistent with our hypothesis, football players 40 years of age and older reported more frequent problems with the ability to control behavior and emotional responses, even after the data were corrected for age. This finding provides additional evidence to suggest that problems with executive function in football players develop or worsen after 40 years of age. Alternatively, differences between age groups could be a cohort effect, reflecting changes in professional

 $^{^{}a}n = 64.$

 $^{^{}b}n = 1050.$

^{*}Significant group differences (index scores, alpha < 0.05; clinical scales, alpha < 0.006).

^aAlpha level = 0.05.

^bAlpha level was adjusted to 0.006.

^{*}Statistically significant.

football over the decades (e.g., development of new protective equipment or differences in individuals that choose to participate). Longitudinal studies are needed to better understand this finding.

Although we believe this study has several strengths, there are also a number of important limitations that require discussion. Scores on the BRIEF-A were compared to normative data, which is not an ideal comparison group for elite athletes. Future studies would benefit from having a comparison group of elite non-contactsport athletes. If results were similar, the findings would further suggest that this executive dysfunction results from repeated mTBI. Because of recent publicity surrounding CTE and the self-referral in our study, it may be that only symptomatic individuals who were concerned about their cognitive functioning volunteered. If this were the case, however, we would have expected to observe very few scores in the normal range. In contrast, nearly one third (31.3%) of the participants had overall scores at or below the expected value for their age (i.e., T score of 50), and for the majority of participants (71.8%), the overall score was below the clinically meaningful threshold (i.e., T score of 65). Because of the inclusion of current and recently retired players, it is possible that some of the executive function problems reported stem from residual postconcussive syndrome. In this case, we would have expected to find higher scores in the younger players. In contrast, we observed higher scores in football players older than 40. Given the retrospective nature of this study, it is impossible to determine whether these findings stem from the effects of participation in football or whether individuals with these characteristics seek out this sport initially. Future prospective studies examining change in executive function over time are needed. Although the BRIEF-A has good convergent validity with other questionnaires, future studies will benefit from also using objective measures of executive functioning in addition to selfreport measures. Finally, we did not exclude individuals with a history of repeated brain trauma from participation in other contact sports or non-sport-related TBIs, which may have also affected the results.

In summary, our results indicate that college and professional football players experience more problems with executive functions in everyday activities than would be expected for their age, and these symptoms appear to develop or worsen in the fifth decade of life. Future longitudinal studies are needed to confirm these initial results. The findings are in accord with a growing body of evidence that participation in football may be associated with the development of cognitive changes and dementia observed in individuals with CTE.

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No competing financial interests exist.

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EXHIBIT 78

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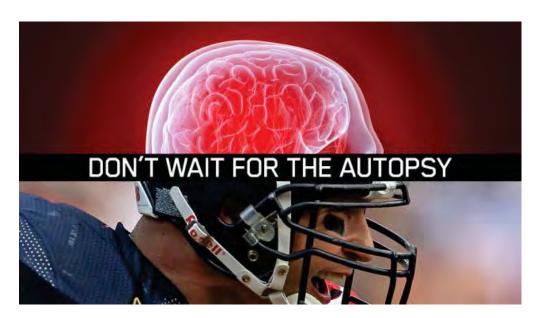
Can Science See Inside An NFL Player's Skull Before It's Too Late? (http://regressing.deadspin.com/5920006/can-science-see-inside-an-nfl-players-skullbefore-its-too-late)

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Chronic traumatic encephalopathy, or CTE, is a diagnosis for dead people. Last month, Junior Seau was found in his home in Oceanside, Calif., with a fatal self-inflicted gunshot wound to the chest. A familiar sequence unfolded: His brain was requested by both the Brain Injury Research Institute and Boston University's Center for the Study of Traumatic Encephalopathy—the two main brain banks chasing damage in former football players. If the family consents, the brain will be sliced open and put under a microscope.

Given Seau's profession and the nature of his demise, the expectation is that the tissues will show a buildup of a protein called tau, creating tangles like the ones found in victims of Alzheimer's disease. But so what? It's one more brain, to go with the 60-plus brains of former players who have already demonstrated postmortem signs of CTE.

The question, after a decade of brain-slicing autopsies, is when any of this will help players before they're dead. Doctors can't just crack open living patients' skulls and lop off slices of their brains to stick under a microscope.

But new research at UCLA is using a cutting-edge biomarker that can attach itself to tau protein tangles so that they show up on PET scans of living subjects. Dr. Gary Small is currently running a pilot study on retired NFL players, imaging their brains in place. If he is successful, his work would reorient the science of head injuries around saving lives instead of merely contextualizing deaths.

"I've always sort of thought of tau imaging as the holy grail on the issue of chronic brain damage, especially CTE," said Dr. Julian Bailes, one of JA3827 the founders of the Brain Injury Research Institute (BIRI).

At The Frontier Of Head-Injury Science

In 2009, the NFL, under heavy fire from the House Judiciary Committee, acknowledged for the first time the long-term consequences of concussions. Since then, the league's ideas about how to protect the living have focused on improving the equipment (better helmets and thighpads) and conspicuously fining defensive players for especially gruesome-looking hits. Non-NFL-affiliated studies have tended to coalesce around those issues. We've measured the force of collisions in mouthguards and pads, and we know the effect of those anti-concussion helmets, too.

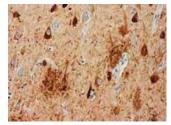
But taken as a whole, the efforts to quell or at least understand CTE have been, to this point, a mix of the cynical, the haphazard, and the fatalistic. There is real value in gathering data about the force of impacts, but the context has often been backward-looking, substantiating science that's no longer really in question. The brain donation and autopsy, for instance, is now more of a mourning rite than a marshalling of fresh evidence.

The NFL has been too busy cosseting itself against any potential legal liability and seeking out second opinions to ask the only question left: What now? The frontiers of CTE research—living patient diagnosis, prevention, risk assessment, *cures*—have been largely left unexplored.

(The NFL did announce a promising study (http://www.nytimes.com/2011/10/04/sports/football/nfl-plans-more-scientific-study-of-concussions.html) late last year, but there have been few details since about when and how it might launch. And it's now been essentially outflanked by a new joint study (http://espn.go.com/blog/ncfnation/post/_/id/62166/b1g-ivy-doing-vital-work-on-concussions) between the Big Ten and the Ivy League that will get underway this year.)

It's not as if the league hasn't had time to do real homework. It's been 10 years since Dr. Bennet Omalu first cut into Mike Webster's brain and discovered CTE, and seven years since Omalu's work appeared in the July 2005 issue of *Neuroscience*, where it was shouted down by the NFL.

Dozens of dead men's brains later, the disbelievers have mostly come around. At its core, CTE is a neurodegenerative brain disease, not much different from Alzheimer's, Parkinson's, or early-onset dementia. It breaks part of your brain, and that affects how you behave and function. But unlike other cases of cognitive decline, we believe we know the root cause: repeated blunt head trauma.



The research could have a profound effect on the NFL and possibly the NCAA. Being able to track the buildup of tau (pictured) is the key to any future serious player safety regime.

While we don't have a cure for CTE's closest analogs, having that starting point makes a big difference. If we can see how the disease unfolds, we have a chance of stopping it. Thus: Gary Small's UCLA research into scanning living subjects. It's funded by BIRI, which was founded by Omalu, Bailes, and Robert Fitzsimmons.

At the center of the study is a patented radioactive biomarker that Small co-invented for diagnosing Alzheimer's disease. The marker attaches itself to both tau protein tangles and amyloid plaques, the two elements necessary to diagnose Alzheimer's. There are other markers that attach to plaques, but this specific marker, [¹⁸F]FDDNP, is the only one known to lock onto tau. In the absolute simplest terms, this is the only known substance in the world that can make CTE show up on a scan in living patients.

PET imaging tech is half a century old, and though FDDNP is relatively new, it's still been around for years. So it's strange to think about the marker being on the cutting edge of a fairly recently discovered brain disease. If the marker can find and pinpoint CTE, why hadn't anyone tried it before now? And for that matter, why isn't it already in use?

More than finding answers, science is about asking the right questions. For something like FDDNP to be tested on NFL players, the thought not only has to occur to someone, but that someone then has to get together someone grants or other funding, and some applicable test subjects.

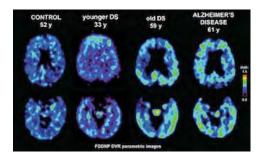
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Small, whose background is in geriatric psychology and Alzheimer's disease, came to CTE research when the chancellor of West Virginia University introduced him to Bailes, who was at WVU at the time. Small's initial study has been funded by BIRI, and Bailes helped refer retired players to Small to try out the scan.

The study is still a pilot program, and there's work to be done before it can be translated into something we can use to diagnose developing cases of CTE—mainly stemming from the fact that FDDNP locks onto not just tau, but the amyloid plaques as well. Still, a biomarker would be perhaps the most important development in the field since Omalu looked at a slide of Webster's brain and saw tau's telltale brown and red splotches (http://www.gq.com/sports/profiles/200909/nfl-players-brain-dementia-study-memory-concussions). Small couldn't share the specific results of his studies because they haven't been published yet, but he was confident. "We think this is going to be a very helpful way to better understand and identify people who are at risk," he said.

"We've autopsied more players than anyone—more than 30 now—and while the science is intriguing, we can only make the diagnosis after death," Bailes said. Small's work, he added, "gives us hope we'll be able to diagnose and identify risk in living patients."

If the scans are effective, they could have a profound effect on the NFL and possibly the NCAA. Being able to track the buildup of tau is the key to any future serious player safety regime. This would likely require regular PET scans—yearly, maybe, or twice a season. An extreme case of CTE—like Webster's—would have a better chance of being caught, especially in the latter stages of a player's career, when his protein levels would be higher.



PET scan, similar to Small's work with CTE, of brain amyloid and tau in adults with Down syndrome.

But even with reliable scans, the risk factors and the rate of tau accumulation would differ from player to player. So Small's group has been looking at ways to refine the risk assessment available to players. "We're looking at genetic factors, a player's position, other behaviors that worsen brain health like smoking or drinking," he said. He's also keeping an eye out for other signs or markers that could be used to identify tau. If, for example, a specific change in a patient's blood were to occur when there's a buildup of tau, maybe a blood test could offer an affordable and less-invasive alternative to the PET scan.

Cheaper alternatives are a crucial point, too. Right now, each scan costs about \$5,000. The price could drop as more companies and groups license FDDNP from UCLA for research. But the scans still probably won't get into the range where the average high school or Division III college could afford to have their players tested multiple times a year.

Knowing When To Stop

In Las Vegas, Dr. Charles Bernick is attacking the same problem from a different angle. Instead of looking for CTE itself, Bernick wants to know how the disease spreads and changes its victim over time. He's wrapping up the first year of an ongoing study tracking the cognitive health of over 100 boxers and MMA fighters, some of whom enlisted at the urging of a family member or spouse who'd started to notice changes in behavior. The goal of the study is to pinpoint when, exactly, a fighter should hang up the gloves.

The Professional Fighters Brain Health Study at the Cleveland Clinic's Lou Ruvo Center for Brain Health pulls from the center's experience with similar diseases, like Parkinson's, to develop a working $modus\ operandi$ for attacking CTE as a traditional brain disease. (The difference, of course, is that those other diseases are a constant deterioration of brain function, while CTE is caused by intermittent brain trauma.) The study uses a combination of MRI scans and computerized cognitive tests—exercises ranging from simple memory tests to questions about what the $\frac{1}{1}$

Bernick hasn't been in contact with the NFL. "It wouldn't be a bad idea in the field for all the oars to be rowing in the same direction," he said. "So if the NFL and hockey and the military were collecting core information, we'd learn a lot faster."

So far, Bernick's team has mapped out a regimen to test fighters at regular intervals for any signs of cognitive decline. The process, which involves computer-based cognitive tests, speech analysis, and thorough MRI scans, closely resembles the tests administered to Alzheimer's and EOD patients.

The MRI in particular is noteworthy. Like PET scans, it's an old technology that can be augmented by asking new and better questions. Specifically, Bernick is trying to hunt down CTE by measuring, comparatively, the size of certain parts of the brain over time, looking for swelling or scar tissue; comparing the brain's conductivity in a resting state to when it's active; and examining blood-vessel buildup, which happens around tau protein.

It's not as easy as just tossing a marker into the brain and firing up a PET scan, but it could be far more scalable outside of the lab.

There are some compromises, though, in the interest of making the test less time-consuming for fighters and other athletes. Unlike Alzheimer's diagnostics, for example, family and friends aren't brought in for cross-referencing on the cognitive tests, and there isn't a genetic analysis of close and distant relatives.

"There's way more that we need to do," Bernick said, "But we had to make it practical. The whole testing takes about two hours to do. It has to be tools you can use anywhere, and it's probably not realistic to expect everyone to go in for a two-hour neuropsych test, but maybe a 20-minute computerized test will do."

The preliminary findings have been suggestive. The fighters were split into three groups: those who had fought for fewer than six years, those who had fought for between six and 12 years, and those who had fought for more than 12 years. They showed a marked decline in cognitive ability from group to group. At six years, there was some drop-off; at 12 years, there was a much larger drop-off.

The six-year groupings were arbitrary, and the data will be shuffled some to try and get a more accurate line of demarcation. Year 2 also introduces retired fighters to the study, so new controls for age will have to be enacted, and more frequent check-ins would obviously be ideal. But for now, it's a starting point. Year over year, the data could be used to pick out different influences: genetic traits that might make humans resistant to CTE, various fighting styles, safe and dangerous layoff periods between fights.

And, of course, there will be post-mortem data. The clinic has made arrangements to supply many of the fighters' brains to one of the large brain banks involved in CTE research.

The important thing to remember about this research—all medical research, really—is that it's not looking to nail down a universal imperative. The surgeon general doesn't tell you the maximum number of cigarettes you're allowed to smoke, or the maximum poundage of cheeseburgers you should eat. So there will not be, say, a scientifically validated eight-year limit on fighting or contact sports. Instead, Bernick is hoping to build a tool for evaluating whether individual fighters should be allowed to continue fighting.

"If you're 38 years old and go to the [Nevada Athletic Commission] to be relicensed, what do they have to go on?" he said. "Maybe the last few fights' performance. But if there was information available to them, they would use it."

Bernick said his group has considered using information from the UCLA PET scans but is holding off because the marker isn't specific to tau itself, and there's still a chance that a tau-only agent will be found.

For their part, the fighters say that they're going to take the results seriously. "If they know that they're sustaining damage to their brain, they would stop," Bernick said. "Maybe a 22-year-old wouldn't say that, but it kind of evolves as you mature. I'm not sure totally people would ignore it. There are regulatory agencies who should be looking at this too. Hypothetically, if you fought eight years, you're required now to get an MRI scan once a year, or a computerized cognitive scan twice a year. If it's more severe, maybe you'd have to stop."

Brain injuries in the state of the state of

In fact, Bailes is working on an absurdly simple accessory that could protect brains from being injured in the first place.



A rendering of the "internal jugular vein compression device." Courtesy Neurosurgery.

Think of it this way: In a collision, the brain is basically driving without a seatbelt or an airbag. While better helmets and the banning of helmet-to-helmet detonations might help keep your skull intact, they would do nothing to stop the brain from smashing into the windshield in even minor collisions. So how do you stop the brain from taking a beating on every routine block, tackle, and other impact—the real killers?

Bailes's answer to this brain slosh amounts to stuffing the whole car full of packing peanuts. His newest research takes groups of rats and puts a small, circular device around their necks, compressing their internal jugular veins. That increases the volume of blood in the skull, which creates added pressure on the brain, locking it in place. In theory, that should keep the brain's movement inside the skull more in line with the skull's own movement, allowing all the new space-age helmets to do their jobs.

So far, Bailes's team has seen a 30 percent increase in cranial pressure, and, after concussing the rats and examining the resulting computer models, an 80 percent drop in the precursors to amyloid protein. "This was only a proof-of-concept pilot study, and it hasn't been proven in humans, but we think the theory is sound," he said. "If it moves forward, we're going to expand to a broader group of patients, and we hope to do that sooner rather than later."

If the research can be replicated and no unforeseen safety concerns pop up—neither of which is guaranteed in research like this—there are already people and players volunteering as test subjects. Why wouldn't there be? If a simple necklace could reduce the accumulation of brain injury, and there is virtually no downside to wearing it, isn't that worth whatever minor discomfort it causes and a few hours a year of testing?

Who Will Pay For The Future?

But for all the practical upside of these projects, it's hard to make ends meet. I asked Bernick where he hopes his project tracking fighters' brains will be in five or 10 years. He replied: "I mean, before anything else, we hope to still be here in five or 10 years. The major goal is to keep the thing going."

The fighter brain-health study costs about \$250,000 a year, but that number's misleading, because so much of what goes into the study—tests, scans, and most crucially, man-hours—is donated by the Cleveland Clinic and its staff. "Without that much help, it would probably cost twice as much." Bernick said.

The NFL's latest collective bargaining agreement sets aside \$100 million to put toward research, much of which is expected to go to brain injury. But so far, only \$1 million has been distributed—to Boston University's CSTE. This issue of funding—in Las Vegas, in tau protein imaging, in all of the studies that haven't or won't get off the ground—is more difficult than it seems.

The Nevada Athletic Commission is deeply interested, and supportive, of the Cleveland study, as are big time fight promoters like Bob Arum's Top Rank and Oscar De La Hoya's Golden Boy. "Everybody at the gyms around here have been very great about this," Bernick said. But despite financial uncertainty, the study hasn't taken money from any of the 13 and interesting dilemma is where you get your funding, and conflicts of

interest," he expanses 12012012016 interest." That's also why he hasn't reached into the NFL's \$100 million pockets yet either, though he absolutely would if it came down to a decision to accept funding or discontinue the study.

For Small's research into the tau protein biomarker, it's partially a matter of getting the word out. Because FDDNP is owned by UCLA, it can be licensed to any pharmaceutical company that wants to use it for studies. (Siemens licensed the marker for non-CTE research for a few years, but ultimately abandoned it.) "That would help drive the cost down, especially for the scans, but we'd still need further grants," Small said. The group has applied for an NIH grant, and submitted several studies and ideas, but it hasn't found any additional funding. Would he consider turning to the NFL and its \$100 million slush fund? "Absolutely," he said, "if there are no strings attached. I understand the financial pressure the NFL is facing, but I'd hope that they want what's best for the players."

What does it mean for the viability of brain-injury research if even tau biomarking—the holy grail—has trouble finding backers? The logical place to stage a project like that would be one of those huge, überprofitable biomedical conglomerates. That's not happening. For competitive reasons, the companies won't talk about business strategies and future plans on the record, but the implication is unmistakable: There is no money in it. Not yet, anyway.

As with the search for a tau protein biomarker, there just isn't the widespread need for continued research in CTE the way there is for other forms of brain deterioration. A representative at one company who asked to not be named explained that, while recent talk about pulling the military into the ongoing brain-injury discussion could go a long way toward making the financials work, it still wouldn't be enough. Despite all the attention it's gotten, a health crisis affecting wealthy young celebrities in America's most popular sport is still only a niche concern.

"It's not like cancer, where your constituency is everyone, or even Alzheimer's, where there are millions," he said. "We just don't get hit in the head very often."

Kyle Wagner is a writer for Gizmodo (http://Gizmodo.com). Top image by Jim Cooke.

EXHIBIT 79

Neuron



Imaging of Tau Pathology in a Tauopathy Mouse Model and in Alzheimer Patients Compared to Normal Controls

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SUMMARY

Accumulation of intracellular tau fibrils has been the focus of research on the mechanisms of neurodegeneration in Alzheimer's disease (AD) and related tauopathies. Here, we have developed a class of tau ligands, phenyl/pyridinyl-butadienyl-benzothiazoles/benzothiazoliums (PBBs), for visualizing diverse tau inclusions in brains of living patients with AD or non-AD tauopathies and animal models of these disorders. In vivo optical and positron emission tomographic (PET) imaging of a transgenic mouse model demonstrated sensitive detection of tau inclusions by PBBs. A pyridinated PBB, [11C]PBB3, was next applied in a clinical PET study, and its robust signal in the AD hippocampus wherein tau pathology is enriched contrasted strikingly with that of a senile plaque radioligand, [11C]Pittsburgh Compound-B ([11C]PIB), [11C]PBB3-PET data were also consistent with the spreading of tau pathology with AD progression. Furthermore, increased [11C]PBB3 signals were found in a corticobasal syndrome patient negative for [11C]PIB-PET.

INTRODUCTION

Hallmark pathologies of Alzheimer's disease (AD) are extracellular senile plaques consisting of aggregated amyloid β peptide

(Aβ) and intraneuronal neurofibrillary tangles (NFTs) composed of pathological tau fibrils, while similar tau lesions in neurons and glia are also characteristic of other neurodegenerative disorders, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), that are collectively referred to as tauopathies (Ballatore et al., 2007). The discovery of tau gene mutations in a familial form of tauopathy, known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), and subsequent studies of transgenic (Tg) mice expressing human tau with or without these mutations, clearly implicate pathological tau in mechanisms of neurodegeneration in AD and related tauopathies (Ballatore et al., 2007). Thus, there is an urgent need for tau imaging techniques to complement A β amyloid imaging methods that now are widely used.

In vivo imaging modalities, as exemplified by positron emission tomography (PET) (Klunk et al., 2004; Small et al., 2006; Kudo et al., 2007; Maeda et al., 2007), optical scanning (Bacskai et al., 2003; Hintersteiner et al., 2005), and magnetic resonance imaging (MRI) (Higuchi et al., 2005), have enabled visualization of Aβ deposits in humans with AD and/or AD mouse models, and there has been a growing expectation that low-molecular-weight ligands for β-pleated sheet structures will also serve as molecular probes for tau amyloids. Although the majority of plaqueimaging agents used for clinical PET studies do not bind to tau lesions (Klunk et al., 2003), at least one radiolabeled β sheet ligand, [18F]FDDNP, enables PET imaging of AD NFTs (Small et al., 2006). However, a relatively low contrast of in vitro autoradiographic and in vivo PET signals for [18F]FDDNP putatively reflecting tau lesions does not allow a simple visual inspection of images for the assessment of tau pathologies in living subjects



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Neuron

Imaging of Tau Pathology in Model Mice and Humans



(Small et al., 2006; Thompson et al., 2009). Thus, better tau radioligands with higher affinity for tau fibrils and/or less nonspecific binding to tissues are urgently needed to complement high-contrast senile plaque imaging agents, including widely studied [¹¹C]Pittsburgh Compound-B ([¹¹C]PiB) (Klunk et al., 2004) and United States Food and Drug Administration-approved [¹8F]florbetapir (Yang et al., 2012). In addition, [¹8F]FDDNP and several other candidate tau probes do not bind to tau inclusions in non-AD tauopathy brains without plaque deposition (Okamura et al., 2005) and therefore can be clinically characterized only in AD patients with comingled Aβ and tau amyloids. Hence, compounds that detect diverse tau aggregates, including tau inclusions in non-AD neurodegenerative diseases and tau Tg models, could be used to interrogate in vivo interactions between exogenous ligands and tau pathologies.

Here, we found that the lipophilicity of β sheet ligands is associated with their selectivity for tau versus A β fibrils and that the core dimensions of these chemicals are major determinants of their reactivity with a broad spectrum of tau aggregates in diverse tauopathies and mouse models of tau pathology. Building on these observations, we developed a series of fluorescent compounds capable of detecting diverse tau lesions using optical and PET imaging in living Tg mouse models of tauopathies. Finally, we identified a radiotracer that produced the highest contrast for tau inclusions in animal PET and used it in exploratory in vivo imaging studies of AD patients, providing clear demonstration of signal intensification in tau-rich regions, in sharp distinction to [11C]PIB-PET data reflecting plaque deposition.

RESULTS

Identification of PBBs as Ligands for Diverse Tau Inclusions in Human Tauopathies

We screened an array of fluorescent chemicals capable of binding to β sheet conformations (see the Compounds subsection in the Experimental Procedures). Fluorescence labeling with these compounds were examined in sections of AD brains bearing AB and tau amyloids (Figures 1A and 2A) and non-AD tauopathy brains characterized by tau inclusions and few or no Aß plaques (Figure 2). Amyloid PET tracers currently used for human PET studies, PIB (Klunk et al., 2004), and BF-227 (Kudo et al., 2007), tightly bound to senile plaques, while they only weakly reacted with AD NFTs (Figures 1A; Figure S1 available online). PET probes reported to selectively label tau aggregates, BF-158 (Okamura et al., 2005) and THK523 (Fodero-Tavoletti et al., 2011), detected AD NFTs (Figures 2A and S1) but microscopically detectable fluorescence signals produced by FDDNP, which are presumed to bind to both Aß and tau fibrils (Small et al., 2006), were consistent with dense cores of classic plaques and distinct from tau lesions (Figures 2A and S1). None of the above-mentioned PET ligands were reactive with tau inclusions in non-AD tauopathies, such as Pick bodies in Pick's disease (Figures 2A and S1) and neuronal and glial fibrillary lesions in PSP and CBD (data not shown). By contrast, these pathologies were intensely labeled with a widely used amyloid dye, thioflavin-S, and a derivative of another classic amyloid dye Congo red, (E,E)-1-fluoro-2,5-bis(3-hydroxycarbonyl-4hydroxy)styrylbenzene (FSB) (Higuchi et al., 2005; Maeda et al., 2007) (Figures 1, 2A, and S1), although these chemicals may not undergo efficient transfer through the blood-brain barrier (BBB) (Zhuang et al., 2001). Because compounds possessing a π-electron-conjugated backbone longer than 13Å exhibited affinities for pathological inclusions in a broad range of tauopathies, we examined binding of additional chemicals with a variety of structural dimensions to tau aggregates and found that affinity for non-AD tau inclusions could be attributed to a core structure with a specific extent ranging from 13 to 19 Å (Figure S1). Based on this view and the known fact that chemicals with a flat and slender backbone could pass through and attach to channel-like accesses in β-pleated sheets (Krebs et al., 2005), we developed a class of compounds, phenyl/pyridinylbutadienyl-benzothiazoles/benzothiazoliums (PBBs), by stretching the core structure of a prototypical fluorescent amyloid dye, thioflavin-T, with two C = C double bond inserts between aniline (or aminopyridine) and benzothiazole (or benzothiazolium) groups (Figure 1B).

All PBB compounds intensely labeled NFTs, neuropil threads, and plaque neurites in AD brains (Figure 1C). Interestingly, the affinity of these PBBs for Aß plaques lacking dense cores was positively correlated with their lipophilicity (Figure 1C), and thereby three potential probes with relatively low logP (log of the octanol/water partition coefficient) values, including PBB3, 2-[4-(4-methylaminophenyl)-1,3-butadienyl]-benzothiazol-5,6-diol (PBB4) and PBB5 (structurally identical to Styryl 7, CAS registry number 114720-33-1), appeared suitable for visualizing tau pathologies in living organisms with reasonable selectivity. High-affinity of PBBs for tau lesions was further demonstrated by fluorometric analyses using AB and tau filaments assembled in a test tube (Table S1; experimental procedures are given in the Supplemental Experimental Procedures). but the most and least lipophilic PBB members displayed similar selectivity for in vitro tau versus Aß pathologies, implying a methodological limitation in screening chemicals for tauselective ligands based on binding to synthetic peptides and recombinant proteins. PBBs and FSB were also shown to label tau inclusions in non-AD tauopathies, such as Pick's disease (Figures 2A and S1), PSP, and CBD (Figure 2B), all of which were immunodetected by an antibody specific for phosphorylated tau proteins (AT8).

In Vitro and Ex Vivo Fluorescence Imaging of Tau Lesions in Tau Tg Mice by PBBs

To obtain in vivo evidence of direct interaction between PBBs and tau lesions, we employed Tg mice expressing a single human four-repeat tau isoform with the P301S FTDP-17 mutation (PS19 line, see Figure S2 for neuropathological features of this Tg strain) (Yoshiyama et al., 2007). Similar to the findings in non-AD tauopathy brains, NFT-like inclusions in the brain stem and spinal cord of PS19 mice were clearly recognized by PBBs (Figures 3A and S1). We then performed ex vivo fluorescence labeling of tau lesions in PS19 mice with intravenously administered PBBs. Brains and spinal cords were removed 60 min after tracer injection, and fluorescence microscopy revealed an intense accumulation of these compounds in fibrillary tau inclusions abundantly seen throughout the sections by



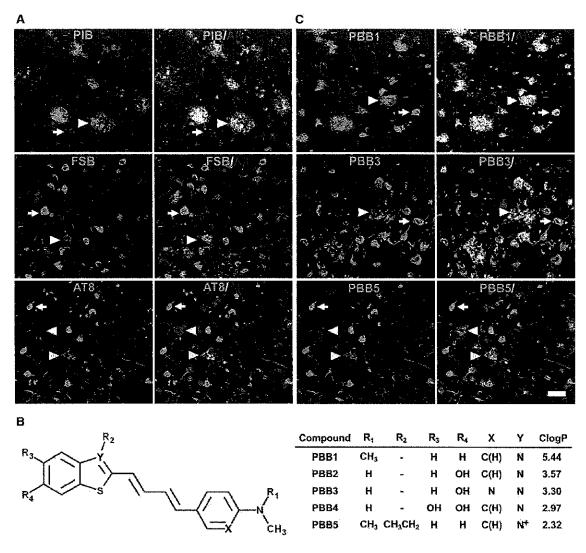


Figure 1. Design and Characterization of PBB Compounds as Potential Imaging Agents for Tauopathies

(A) Confocal fluorescence images of frontal cortex sections from an AD patient. Following fluorescence labeling (pseudocolors are converted to green) with PIB (top row) and FSB (middle row), the samples were immunostained with an antibody against AβN3(pE) (red in the right column). PiB intensely labeled Aβ plaques (white arrowheads) but did not clearly label NFTs (arrows). By contrast, NFTs and neuropil threads were intensely labeled by FSB, whereas the staining of diffuse plaques was negligible. A section was also doubly immunolabeled (bottom row) with AT8 (green) and anti-AβN3(pE) antibodies (red in the right panel), to demonstrate the abundance of tau and Aβ amyloids in this area. Yellow arrowheads indicate tau-positive dystrophic neurites associated with senile plaques. (B) Structures of PBBs. Neutral benzothiazoles (PBB1-4) are newly synthesized chemicals, and a charged benzothiazolium, PBB5, is identical to a commercially available near-infrared laser dye.

(C) Confocal fluorescence images of PBBs (pseudocolors are converted to green) and AβN3(pE) (red in the right column) staining in sections adjacent to those displayed in (A). The intensity of plaque staining (arrowheads) relative to that of NFTs (arrows) was positively associated with the lipophilicity of PBBs. As compared with PBB1 (top row) staining, labeling of diffuse plaques with PBB3 (middle row) was substantially attenuated. PBB5 was nearly unreactive with diffuse plaques (bottom row), and subsequent double immunofluorescence staining of the same section (bottom row in C) illustrated good agreement of PBB5 labeling with the distribution of AT8-positive NFTs.

Scale bar, 50 µm (A and C). See also Figure S1 and Table S1.

staining with thioflavin-S, FSB, and AT8 (Figure 3B). On the other hand, no overt in vitro (Figure 3A) or ex vivo (data not shown) fluorescence of these ligands was noted in the corresponding regions of non-Tg wild-type (WT) mice. Consistent with these observations, two-photon laser scanning fluorescence microscopy of ex vivo samples demonstrated somatic and neuritic staining of a subset of tangle-bearing neurons with intravenously injected 2-[4-(4-methylaminophenyl)-1,3-butadienyl]-benzothia-

zol-6-ol (PBB2) and PBB4 in unsliced spinal cord blocks from PS19 mice (Figure 3B).

In Vivo Macroscopic and Mesoscopic Optical Detection of Fibrillar Tau Pathologies in a Mouse Model Using PBB5

We next characterized PBBs with the use of in vivo fluorescence imaging modalities, which permitted a quick assessment of



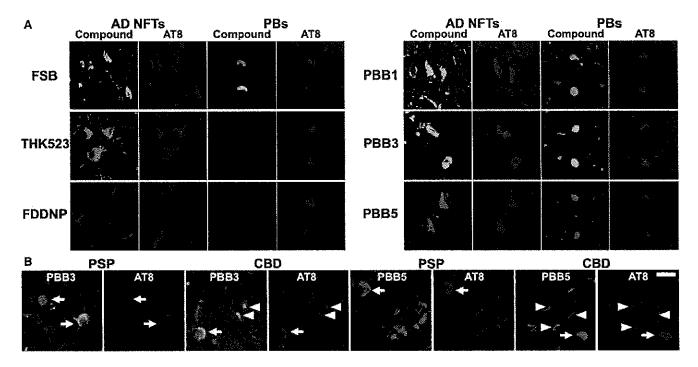


Figure 2. Binding of Tau Ligands to Tau Lesions in AD and Non-AD Tauopathy Brains

(A) Double fluorescence staining of AD NFTs and Pick bodies (PBs) in Pick's disease with PBBs, other tau ligands, and anti-phospho-tau antibody (AT8). FSB and PBBs sensitively captured AD NFTs and PBs. AD NFTs were labeled with THK523. Meanwhile, PBs were not visualized by these compounds. NFTs and PBs were barely recognizable by using FDDNP.

(B) Double fluorescence staining of neuronal tau inclusions (arrows) in PSP and CBD and putative astrocytic plaques (arrowheads) in CBD. A substantial portion of tau fibrils in neurons were captured by PBB3 and PBB5, but a much smaller subset of phosphorylated tau aggregates in astrocytic plaques were labeled with these compounds.

Scale bar, 20 μm (A and B). See also Figures S2 and S3.

candidate chemicals without the need for radiolabeling. Because PBB5 is fluorescent, with peak excitation and emission wavelengths in a near-infrared range (Table S1), this compound is applicable to in vivo optical imaging of tau deposits in laboratory animals. To examine this possibility, fluorescence images were obtained from living mice over a time course following intravenous PBB5 injections using a small animal-dedicated system permitting the intravital observation of fluorescence signals at magnifications varying between macroscopic and microscopic levels. Tail vein administration of PBB5 in PS19 mice revealed strong fluorescence relative to non-Tg WT mice in the central nervous system (CNS) above the slit between the base of the skull and first vertebra, through the skin and connective tissues overlaying the cisterna magna (Figures S3A-S3D), suggesting a concentration of this tracer in the PS19 spinal cord. In line with this in vivo observation, the hindbrain and spinal cord of PS19 mice, which were dissected out at 2 hr after the injection of PBB5, exhibited increased retention of this compound compared to non-Tg WT mice (Figures S3E-S3G).

In vivo optical imaging of tau Tg mice was subsequently performed using a device equipped with a pulsed diode laser and a photomultiplier tube to detect deep signals through the skull. Elevated levels of fluorescence intensity were found in homogenized brain stem samples collected from PS19 mice at 20 hr after the intravenous tracer administration (Figure S4A), indicating a long-lasting in vivo binding of PBB5 to tau fibrils. To support

the ex vivo evidence, fluorescence intensity was noninvasively analyzed in living PS19 and non-Tg WT mice treated with PBB5. The mice, with their heads shaved in advance, were prescanned, and autofluorescence signals were detected at a relatively high level in an area corresponding to the frontal forebrain. Using these baseline signals as landmarks, regions of interest (ROIs) were defined in the frontal cortex, brain stem, and spinal cord (Figure 4A). The near-infrared fluorescence was notably increased immediately after the intravenous injection of PBB5 (Figure S4C), and the fluorescence in the brain stem and spinal cord ROIs of PS19 mice much exceeded that in WT mice at 30 min (Figure 4B). Fluorescence intensity in the frontal cortex ROI, normalized on the basis of integration time and laser power, was lower in PS19 mice than in WT mice over 120 min after tracer injection (Figure S4B), which may reflect impaired CNS delivery of the tracer in Tg mice due to degenerative changes (see Figures S4C-S4L for details), and thereafter this became almost equivalent between the two genotypes (Figure S4B). Meanwhile, persistent retention of the signals in the brain stem and spinal cord ROIs of PS19 mice was observed beyond 240 min (Figures 4B and S4B). A more quantitative index comparable among different mice was determined by calculating the target-tofrontal-cortex ratio of fluorescence intensity and was shown to increase over time particularly in PS19 mice (Figures 4C and 4D). This ratio was significantly greater in PS19 mice than in WT mice at 240 min (Figure 4E), beyond which the difference



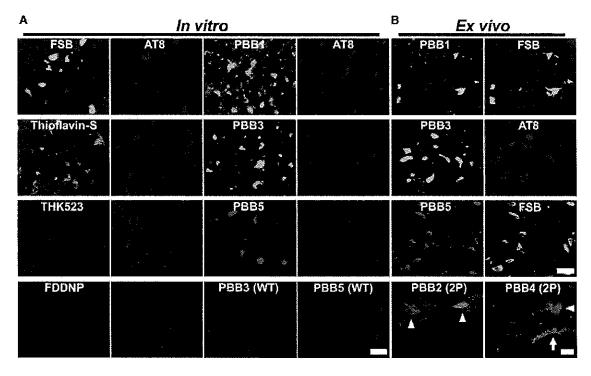


Figure 3. In Vitro and Ex Vivo Labeling of NFTs in PS19 Mice with PBB Compounds

(A) Double fluorescence staining of intraneuronal tau aggregates in postmortem brain stem slices of a 12-month-old PS19 mouse with PBB, other amyloid ligands, and anti-phospho-tau antibody (AT8).

(B) Binding of intravenously administered PBBs (0.1 mg/kg PBB5 and 1 mg/kg PBB1 and PBB3) to NFTs in PS19 mice at 10–12 months of age. The tissues were sampled at 60 min after tracer administration. The brain stem (top row) and spinal cord (second and third rows from the top) sections abundantly contained neurons showing strong fluorescence (left), and subsequent staining with FSB or AT8 (right) indicated that these cells were laden with tau amyloid fibrils (right). Putative intraneuronal tau inclusions in unsectioned spinal cords (arrowheads in the bottom row) removed from PS19 mice at 60 min after intravenous injection of PBB2 and PBB4 were also clearly visible by using a two-photon (2P) fluorescence microscopic system. Arrow in the bottom row indicates a cluster of autofluorescence signals from blood cells.

Scale bars, 25 μ m (A), 30 μ m (top to third rows in B), and 20 μ m (bottom row in B).

between the two lines of mice became nearly constant (Figures 4C and 4D). The intensity ratio of the spinal cord ROI to the frontal cortex in PS19 mice at 240 min was also significantly correlated with the abundance of NFTs stained with FSB (Figure 4F), but such correlations were not statistically significant in the brain stem (Figure 4F), implying limitations of the intensitometry in some brain regions below the cerebellum and fourth ventricle.

Intravital Imaging of Individual Tau Inclusions by PBB3 and Two-Photon Laser Scanning Fluorescence Microscopy

Two-photon excitation microscopy, which enables optical sectioning, potentially up to 1 mm deep, in living tissues, could be utilized to visually demonstrate transfer of a fluorescent probe from the plasma compartment into the cytoplasm of CNS neurons and binding of the probe to intraneuronal tau inclusions. We therefore captured fluorescence signals from intravenously administered PBB3 by in vivo two-photon laser scanning microscopic imaging of the spinal cord of laminectomized PS19 mice. Within 3 s of PBB3 injection, green fluorescence signals emerged in blood vessels prelabeled with red with intraperitoneal treatment using sulforhodamine 101 and subsequently diffused from the vasculatures to the spinal cord parenchyma

over the next few minutes (Figures 5A–5F). These diffuse signals declined thereafter due to the clearance of PBB3 from the tissue, whereas intense labeling of putative tau inclusions with green fluorescence appeared in a subpopulation of large cells morphologically identified as neurons at 3–5 min after PBB3 injection (Figures 5G and 5H). These intracellular PBB3 fluorescent signals were not found in the spinal cord of WT mice (Figure 5I). As the BBB of the brain and spinal cord are presumed to be identical, the two-photon microscopic data obtained here provide compelling evidence that PBB3 rapidly transits the BBB and neuronal plasma membranes, where it binds to intraneuronal tau inclusions. Accumulation of injected PBB3 in AT8-positive, NFT-like lesions of Tg mice was postmortemly confirmed by ex vivo microscopy (Figures 5J and 5K).

Autoradiographic and PET Imaging of Tau Lesions in PS19 Mice by Radiolabeled PBBs

We investigated the kinetic properties of PBBs by high-performance liquid chromatography (HPLC) analyses of plasma and brain samples collected from non-Tg WT mice treated with these ligands. Following intravenous administration, PBB5 was rapidly converted into a major metabolite, which at 5 min was found at high levels in both plasma and brain extracts. Subsequent liquid



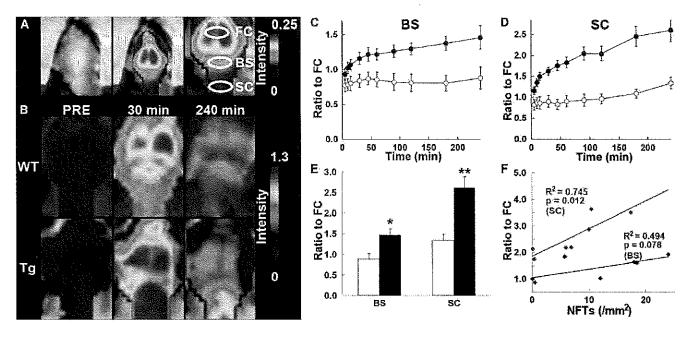


Figure 4. Noninvasive Near-Infrared Imaging of Tau Pathology in Living Tau Tg Mice Using Pulsed Laser Optics and PBB5

(A) Baseline autofluorescence signals (middle) are overlaid on the visible background image of a shaven non-Tg WT mouse head (left). Ellipsoidal ROIs are defined above the frontal cortex (FC), brain stem (BS), and cervical spinal cord (SC) guided by a relatively intense emission from the FC region (right).

(B) Fluorescence intensity maps in 12-month-old WT (top) and PS19 (Tg; bottom) mice before and at 30 and 240 min after the intravenous administration of PBB5 (0.1 mg/kg). The intensity maps (A and B) are normalized by the FC ROI value at 30 min after tracer injection. Long-lasting retention of the tracer was noted in the BS and SC ROIs of the Tg mouse.

(C and D) Target-to-FC ratios of fluorescence intensity in the BS (C) and SC (D) ROIs over the image acquisition time in the WT (open circles; n=7) and PS19 (closed circles; n=7) mice. There were significant main effects of time, region, and genotype in two-way, repeated-measures ANOVA (time, $F_{(11, 132)} = 17.6$, p < 0.001; region, $F_{(1, 12)} = 29.9$, p < 0.001; genotype, $F_{(1, 12)} = 23.6$, p < 0.001).

(E) Target-to-FC ratios in the BS and SC ROIs of the WT (open columns) and tau Tg (closed columns) mice at 240 min after tracer injection. *p < 0.05; **p < 0.01; two-way repeated-measures ANOVA with Bonferroni's post hoc analysis.

(F) Scatterplots of target-to-FC ratios at 240 min versus the number of FSB-positive NFTs per unit area of postmortem 20 μm tissue slices in BS (blue symbols) and SC (red symbols) ROIs of tau Tg mice. Solid lines represent regressions; p values were determined by t test. Vertical bars in the graphs represent SEs. See also Figures S3 and S4.

chromatography-mass spectrometry (LC-MS) assays suggested that the major metabolite was likely a reduced, electrically neutralized derivative of PBB5 (Figures S5A and S5B). Besides transventricular uptake of unmetabolized PBB5 as implied above, this uncharged form incapable of emitting nearinfrared light could readily penetrate the BBB, as well as cell membranes, and thereafter could be reoxidized into its original form, thereby enabling it to bind to tau fibrils, particularly at sites exposed to oxidative stress in pathological conditions. In addition, PBB4 was promptly converted to metabolites capable of entering the brain. Finally, studies of PBB2 and PBB3 showed that they exhibited reasonable biostability and sufficient entry into and clearance from the brain. Indeed, HPLC assays demonstrated that fractions of unmetabolized PBB2 and PBB3 in mouse plasma were 23.5% and 16.3%, respectively, at 3 min after intravenous administration and were 4.6% and 2.8%. respectively, at 30 min. There were also no metabolites of PBB2 and PBB3 detectable in the mouse brain at 3 and 30 min.

We then radiolabeled PBB2 and PBB3 with ¹¹C to conduct autoradiographic and PET assays using PS19 mice. In vitro autoradiography using frozen tissue sections showed binding of these radioligands to the brain stem of PS19 mice and neocortex of AD patients (Figure 6A). As expected from their lipophilicities,

[11C]PBB3 yielded high-contrast signals with less nonspecific labeling of myelin-rich white matter than did [11C]PBB2, and the accumulation of [11C]PBB3 in pathological regions was nearly completely abolished by the addition of nonradioactive compounds. Similarly, ex vivo autoradiographic studies demonstrated that intravenously administered [11C]PBB3 selectively labeled the brain stem and spinal cord of PS19 mice harboring neuronal tau inclusions, whereas tau-associated [11C]PBB2 radiosignals were less overt because of a considerable level of nonspecific background (Figure 6B; Figures S6C-S6F). Finally, in vivo visualization of tau lesions in PS19 mouse brains was enabled by a microPET system using these two tracers (Figures 6C, S6A, and S6B). Following intravenous injection, [11C]PBB3 rapidly crossed the BBB and unbound and nonspecifically bound tracers were promptly washed out from the brain with a half-life of ~10 min (left panel in Figure 6E). The retention of [11C]PBB3 signals in the brain stem of 12-month-old PS19 mice lasted over the imaging time (90 min), producing a pronounced difference from that in age-matched non-Tg WT mice (left panel in Figure 6E). By selecting the striatum as a reference region lacking tau deposits, the target-to-reference ratio was estimated for the brain stem, with the value in PS19 mice peaking at around 70 min, contrasting with its continuous decrease over



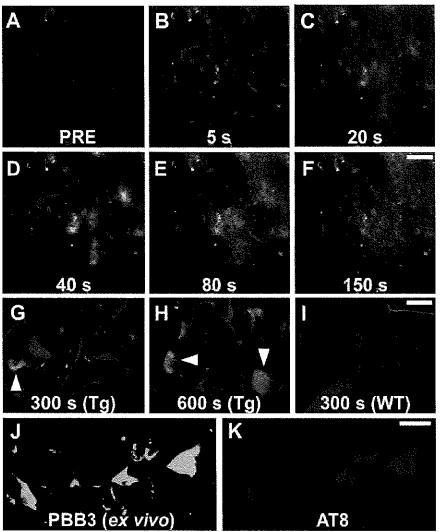


Figure 5. Real-Time Two-Photon Laser Scanning Images of PBB3 Diffusing from Vessels, Binding to Intraneuronal Tau Inclusions, and Clearing from Spinal Cord

(A–H) A maximum projection of fluorescence in a 3D volume of the spinal cord of a living PS19 mouse at 12 months of age before (A) and at various time points after (B–H) intravenous administration of PBB3 (1 mg/kg). Blood vessels were labeled with sulforhodamine 101 (red) intraperitoneally injected at 15 min before PBB3 administration. Green fluorescence indicates a rapid transfer of PBB3 from the plasma to tissue parenchyma (B–E) and subsequent washout from the tissue (F). Background PBB3 signals were further attenuated beyond 300 s, whereas somatodendrific labeling by this compound was observed in a subset of neurons (arrowheads in G and H).

(I) Fluorescence image of WT spinal cord at 300 s after PBB3 injection demonstrates no overt retention of the tracer in the tissue.

(J and K) Ex vivo microscopy for a brain stem section of the same Tg mouse. Tissues were obtained at 60 min after PBB3 injection, Signals of intravenously administered PBB3 (J) overlapped with AT8 immunoreactivity (K).

Scale bars, 50 μm (A–F), 25 μm (G–I), and 25 μm (J and K).

of [11C]methoxy-PBB5 ([11C]mPBB5; Figure S5C). PET images demonstrated complex pharmacokinetics of

[11C]mPBB5 (Figures S5D and S5E), and the difference in the specific radioligand binding between Tg and WT mice was small relative to the [11C]PBB3-PET data (Figure S5F). After taking all of these findings into consideration, [11C]PBB3 was selected as the most suitable ligand for in vivo PET imaging of tau pathology in tau Tg mice and human subjects.

Notably, the hippocampus of many PS19 mice was devoid of overt [11C]PBB3 retention (Figure 6C), although a pronounced

Notably, the hippocampus of many PS19 mice was devoid of overt [11C]PBB3 retention (Figure 6C), although a pronounced hippocampal atrophy was noted in these animals. This finding is in agreement with the well-known neuropathological features of PS19 mice in the hippocampus, because the accumulation of AT8-positive phosphorylated tau inclusions results in the degeneration of the affected hippocampal neurons prior to or immediately after NFT formation, followed by the clearance of their preNFTs or NFTs that are externalized into the interstitial CNS compartment (Figure S2). To explore the feasibility of our imaging agents in studies with other tauopathy model mice, we also performed fluorescence labeling with PBBs for brain sections generated from rTg4510 mice (Santacruz et al., 2005; the Supplemental Experimental Procedures). As reported elsewhere (Santacruz et al., 2005), these mice developed numerous thioflavin-S-positive neuronal tau inclusions in the neocortex and hippocampus, and reactivity of these lesions with PBBs was demonstrated by in vitro and ex vivo fluorescence imaging (Figure S7),

60 min in WT mice (right panel in Figure 6E). The mean ratio at 45-90 min was increased by 40% in 12-month-old PS19 mice as compared with age-matched WT mice (p < 0.01 by t test). The agreement between localizations of PET signals and tau inclusions in PS19 mice was proven by postmortem FSB staining of brain sections from scanned mice (Figure 6D). Significantly, the mean target-to-reference ratio in the brain stem quantified by PET correlated closely with the number of FSB-positive inclusions per brain section in the same region of the postmortem sample (p < 0.001 by t test; data not shown). $[^{11}C]PBB2$ exhibited slower clearance from the brain and higher nonspecific retention in myelin-rich regions than [11C]PBB3 (Figure S6G), resulting in insufficient contrast of tau-bound tracers in the brain stem of PS19 mice and a small difference in the target-to-reference ratio of radioactivities between PS19 and WT mice (8% at 45-90 min; p < 0.05 by t test; Figure S6H) relative to those achieved with [¹¹C]PBB3.

As radiolabeling at the dimethylamino group in PBB5 with ¹¹C was unsuccessful, ¹¹C-methylation of a hydroxyl derivative of this compound was performed, leading to the production

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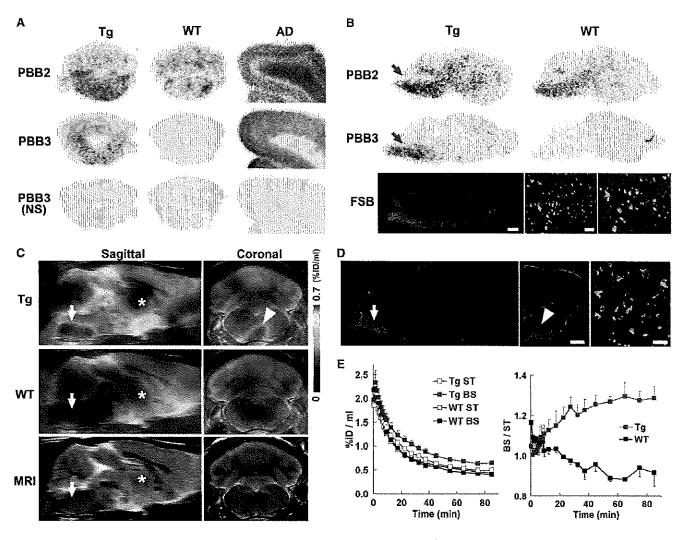


Figure 6. PET and Autoradiographic Detection of Tau Pathologies in PS19 Mice Using [11C]PBB2 and [11C]PBB3

(A) In vitro autoradiograms of PS19 and non-Tg WT hindbrains (coronal sections) and AD frontal cortex. Fibrillar aggregates in the mouse brain stem and AD gray matter produced intense radiolabeling with both tracers, but nonspecific background signals were also observed at a considerably high level with the use of [¹¹C]PBB2. Binding of [¹¹C]PBB3 was profoundly abolished by the addition of nonradioactive PBB3 (10 μM).

- (B) Autoradiographic labeling with intravenously injected [¹¹C]PBB2 and [¹¹C]PBB3 in PS19 (Tg) and WT mice. The brains were removed at 45 min after injection and were cut into sagittal slices. The autoradiographic section of PS19 brain was also stained with FSB. Arrows indicate the brain stem containing numerous tau inclusions displayed at intermediate and high magnifications.
- (C) Sagittal and coronal PET images generated by averaging dynamic scan data at 60–90 min after intravenous administration of [11C]PBB3. The images are overlaid on the MRI template (images of the template alone are presented at the bottom). Arrows and asterisks indicate the brain stem and striatum, respectively, and arrowhead denotes intense radiolabeling in the medial brain stem of the PS19 mouse.
- (D) FSB staining of PS19 mouse brain shown in (C). Sagittal (left) and coronal (middle) images and a high-power view of fibrillar inclusions (right) are displayed. Corresponding to high-level retention of [11C]PBB3 in PET scans, abundant FSB-positive lesions were found in the medial brain stem (arrow and arrowhead). (E) Time-radioactivity curves (left) in the striatum (ST) and brain stem (BS) and BS-to-ST ratio of radioactivity (right) over the imaging time in PS19 (Tg; red symbols) and WT (black symbols) mice (n = 5 each). Vertical bars in the graphs denote SEs.

Scale bars, 1 cm (A and B, top, middle, and bottom left panels); 1 cm (C and D, left and middle panels); 100 μm (B, bottom middle panel); and 100 μm (B, bottom right panel and D, right panel). See also Figures S5, S6, and S7.

Detection of Tau Pathologies in Living Brains of AD Patients by Comparative PET Imaging with [11C]PBB3 and [11C]PIB

In order to compare the bindings of [¹¹C]PBB3 and [¹¹C]PIB to tau-rich regions in the human brain, in vitro autoradiography was carried out with sections of AD and control hippocampus. A notable difference in labeling between these two radioligands

was observed in the CA1 sector and subiculum of the AD hippocampus, where fibrillar tau aggregates predominantly localized to NFTs and neuropil threads (Figure 7A).

We subsequently conducted an exploratory clinical PET study for patients with probable AD (n = 3) and age-matched cognitively normal control (NC) subjects (n = 3). All AD patients exhibited a marked increase in the retention of $[^{11}C]PIB$ in



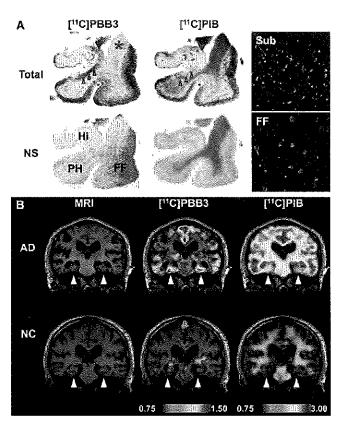


Figure 7. Accumulation of [11C]PBB3 in the Hippocampal Formation of AD Patients Revealed by In Vitro Autoradiography and In Vivo PET (A) Autoradiographic labeling of adjacent brain sections from an AD patient with 10 nM of [11C]PBB3 (left) and [11C]PIB (middle). The slices contain the hippocampus (Hi), parahippocampal gyrus (PH), fusiform gyrus (FF), and white matter (asterisks). Total binding (top) of [11C]PBB3 and [11C]PIB was markedly abolished (bottom) by addition of nonradioactive PBB5 (100 µM) and thioflavin-S (10 µM), respectively, except for the nonspecific (NS) labeling of white matter with [11C]PIB, The hippocampal CA1 sector and subiculum displayed intense [11C]PBB3 signals without noticeable binding of [11C]PIB, and binding of [11C]PBB3 in cortical areas flanking the collateral sulcus (identified by a red dot) and hippocampal CA2 sector (arrows) was also abundant relative to that of [11C]PIB. FSB staining of amyloid fibrils in the sections used for autoradiography indicated the predominance of NFTs and diffuse plaques in the hippocampal subiculum (Sub) and fusiform gyrus (FF), respectively (right panels), supporting the strong reactivity of [11C]PBB3 with AD NFTs.

(B) MRI (left) and PET imaging with [¹¹C]PBB3 (middle) and [¹¹C]PIB (right) performed in the same AD (top) and normal control (NC; bottom) subjects. Coronal images containing the hippocampal formation (arrowheads) are displayed. [¹¹C]PBB3- and [¹¹C]PIB-PET images were generated by estimating SUVRs at 30–70 min and 50–70 min after radiotracer injection, respectively, and were superimposed on individual MRI data. In the hippocampal formation, prominently increased retention of [¹¹C]PBB3 in the AD patient was in sharp contrast to the modest or negligible changes in [¹¹C]PIB binding as compared with NC. Scale ranges for SUVRs were 0.75–1.50 ([¹¹C]PBB3) and 0.75–3.00 ([¹¹C]PIB).

See also Figure S9.

plaque-rich areas, and all NC were negative for this PET assay. These subjects then received a [11C]PBB3-PET scan, and the [11C]PBB and [11C]PBB3 images were compared in the same individuals. Intravenously injected [11C]PBB3 was delivered to the brain tissue despite its relatively rapid metabolism in humans

(Figures 9A and 9B), Unlike [11C]PIB, [11C]PBB3 showed minimal nonspecific binding to white matter and other anatomical structures with high myelin content, although it accumulated in dural venous sinuses in control and AD brains (Figures 7B, 8, and 9B). Time courses of regional radioactivity (Figures 9C and 9D; Figures S8A and S8B) and the standardized uptake value ratio (SUVR) to the cerebellum (Figures S8C and S8D) demonstrated accumulation of [11C]PBB3 in several brain regions of AD patients as compared to controls (definition of these VOIs is indicated in Figure S8E). In agreement with autoradiographic findings, binding of [11C]PBB3 to the medial temporal region, including the hippocampus, contrasted strikingly with the lowlevel retention of [11C]PIB in this area (Figure 7B). There was a slight increase in the retention of [11C]PBB3 primarily in the medial temporal region of a control subject with a loss of several points in Mini-Mental State Examination (MMSE) (subject 3 in Figure 8), appearing similar to the tau pathology at Braak stage III/IV or earlier (Braak and Braak, 1991), distinct from the lack of enhanced [11C]PIB signals. Indeed, mild increase of medial temporal SUVR (Figure 9E) contrasted with unremarkable change in lateral temporal and frontal SUVRs in this subject (Figures 9G and 9H). Signals of [11C]PBB3 were also intense mainly in the limbic region of a subject with early AD (subject 4 in Figure 8), but profound and moderate increases of SUVRs were also observed in the lateral temporal and frontal cortices, respectively, of this case (Figures 9G and 9H), resembling the localization of tau deposits at Braak stage V/VI (Braak and Braak, 1991). With the further cognitive decline as scored by MMSE (subjects 5 and 6 in Figure 8), additional increase in the retention of [11C]PBB3 was found in the medial temporal region, precuneus, and frontal cortex (Figures 9E, 9F, and 9H). Meanwhile, a substantial decline of [11C]PBB3 binding was noted in the lateral temporal cortex of subject 6 (Figures 8 and 9G). The SUVRs in the medial temporal region, precuneus, and frontal cortex were consequently well correlated with the decline of MMSE scores (Figures 9E, 9F, and 9H), In distinction with [11C]PBB3-PET data, there was no overt association between the binding of [11C]PIB and disease severity in AD patients (Figure 8), consistent with previous observations. These data support the potential utility of [11C]PBB3 for clarifying correlations between the distribution of tau deposition and the symptomatic progression of AD,

As in vitro fluorescence staining indicated that PBB3 was reactive with not only tau lesions but also several types of senile plaques, particularly dense core plaques, density of binding sites, and affinity of [11C]PBB3 for these sites were quantified by autoradiographic binding assays with hippocampal and neocortical sections of AD brains enriched with NFTs and senile plaques, respectively. These analyses demonstrated that specific radioligand binding sites were primarily constituted by high-affinity, low-capacity binding components in NFT-rich regions and low-affinity, high-capacity binding components in plaque-rich regions (Figures S9A and S9B). A subsequent simulation for radioligand binding in an area containing these two types of binding sites at a ratio of 1:1 indicated that the selectivity of [11C]PBB3 for NFTs versus plagues may be inversely associated with concentration of free radioligands (Figure S9C). In a range of free concentration in the brain achievable

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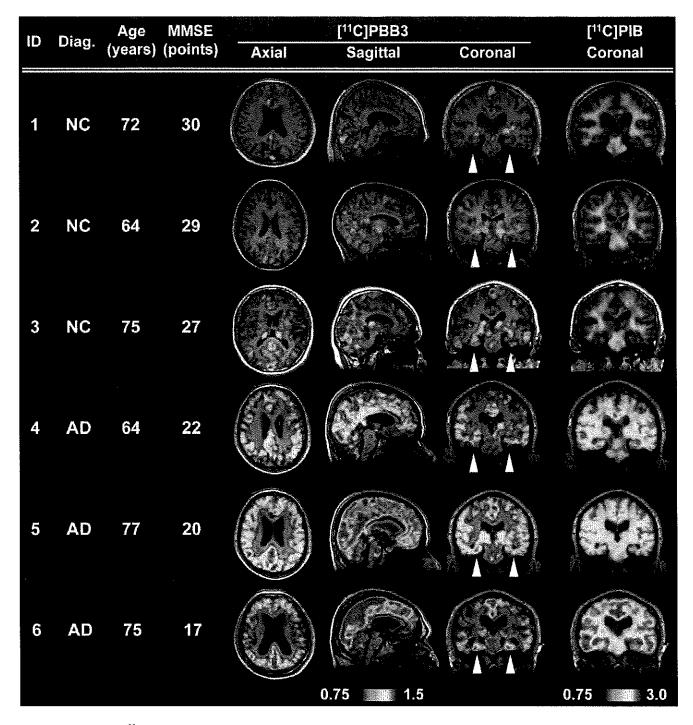
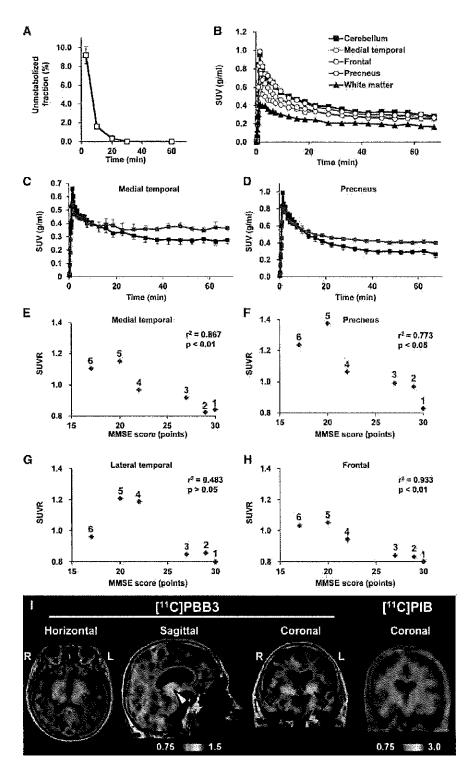


Figure 8. Orthogonal [11C]PBB3-PET Images in All Human Subjects Examined in the Present Exploratory Clinical Study

Data are displayed as parametric maps for SUVR. The [11C]PBB3 binding to the hippocampal formation (arrowheads) was increased consistently in AD patients in contrast to minimum radiotracer retention in normal control (NC) subjects with MMSE scores of 29–30 points (subjects 1 and 2). Another NC subject with an MMSE score of 27 points (subject 3) was negative for [11C]PIB-PET but exhibited slight accumulation of radiotracer signals primarily around the hippocampus, resembling fibrillar tau deposition at Braak stage III/IV or earlier. Sagittal slices around the midline illustrate that radioligand signals were the most intense in the limbic system but began to expand to the neocortex in a patient with the mildest AD (subject 4), in agreement with the tau pathology at Braak stage V/VI, and was further intensified in most neocortical areas, corresponding to Braak stage VI, apparently as a function of the disease severity assessed by MMSE (subjects 5 and 6). The AD patient with the lowest MMSE score (subject 6) displayed a less profound increase of [11C]PBB3 retention in the lateral temporal and parietal cortices than did the other two AD cases, and this is attributable to marked cortical atrophy in this individual and/or toxic loss of tau-bearing neurons in these brain areas at an advanced pathological stage. In contrast to the spatial profiles of [11C]PBB3 binding, the distribution of [11C]PIB signals appeared unchanged among AD subjects. See also Figure S9.





at a pseudoequilibrium state in human PET imaging (<0.2 nM), [11 C]PBB3 is presumed to preferentially bind to tau lesions relative to in vitro autoradiographic (\sim 1 nM) and fluorescence (>100 nM) labeling.

We also estimated contribution of [11C]PBB3 bound to dense core plaques to total radiosignals in the neocortical

Figure 9. Pharmacokinetic Profiles of [11C]PBB3 Administered to Humans and PET Images of a Patient Clinically Diagnosed as Having Corticobasal Syndrome

(A) Time course of unmetabolized [11C]PBB3 fraction in plasma following intravenous radio-tracer injection. The plot was generated by averaging data from six individuals.

(B) Time-radioactivity curves in different brain regions of cognitively normal control subjects over 70 min after intravenous injection of [11C]PBB3. Data were generated by averaging values in two individuals and are presented as standard uptake values (SUVs).

(C and D) Comparisons of time-radioactivity curves in the medial temporal region (C) and precuneus (D) of normal controls (black symbols and lines; n=3) and AD patients (red symbols and lines; n=3).

(E–H) Scatterplots illustrating correlation of SUVRs with MMSE scores in the medial temporal region (E), precuneus (F), and lateral temporal (G) and frontal (H) cortices. Numbers beside symbols denote subject ID as indicated in Figure 8. Coefficients of determination (r^2) and p values by t test are displayed in graphs.

(I) [11C]PBB3- and [11C]PIB-PET images in a subject with clinical diagnosis of corticobasal syndrome, Images were generated as in Figures 7 and 8. Accumulation of [11C]PBB3 was noticeable in the basal ganglia (red arrowheads) with right-side dominance and an area containing the thalamus and midbrain (yellow arrowhead).

Vertical bars in the graphs represent SEs. See also Figures S8 and S9.

gray matter of AD patients, by conducting autoradiography and FSB histochemistry for the same sections. Radiolabeling associated with dense cored plaques accounted for less than 1% and 3% of total gray matter signals in the temporal cortex and precuneus, respectively (Figures S9D-S9H), Moreover, fluorescence labeling of adjacent sections with PBB3 demonstrated that approximately 2% and 5% of total gray matter fluorescence signals were attributable to PBB3 bound to dense core plagues in the temporal cortex and precuneus, respectively. Hence, dense cored plagues were conceived to be rather minor sources of binding sites for [11CIPBB3,

Finally, PET scans with [11C]PBB3 and [11C]PIB were conducted for a subject clinically diagnosed as having corticobasal syndrome. Retention of [11C]PIB stayed at a control level, but notable accumulation of [11C]PBB3 was observed in the neocortex and subcortical structures (Figure 9I), providing evidence for in vivo detection of tau lesions in plaque-negative

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tauopathies. Interestingly, right-side dominant [11C]PBB3-PET signals in the basal ganglia were consistent with laterality of atrophy in this area (Figure S8F). These findings may also be associated with a right-side dominant decrease in cerebral blood flow and left-side dominant motor signs in this patient.

DISCUSSION

Here, we report our efforts to develop BBB-penetrant ligands that are capable of binding to and visualizing intracellular tau aggregates in AD and non-AD tauopathies. These compounds may accordingly be useful for the differential diagnosis of neurological conditions in elderly subjects on the basis of the distribution of tau lesions, thereby opening up novel avenues for research in elucidating mechanisms of tau-mediated neurodegeneration, as well as tau-focused biomarkers and therapies.

Despite numerous efforts to develop imaging ligands to visualize tau pathologies in the brains of patients with AD and related tauopathies, the urgent need for these tau biomarkers remains largely unmet. To address this significant challenge, we also took advantage of a multimodal imaging system, which facilitates a quick and label-free validation of candidate compounds in terms of their transfer to the brain and retention in tau-rich regions. In addition, subcellular-resolution imaging optics exemplified by two-photon laser scanning microscopy provided proof of the rapid transfer of intravenously administered potential tau pathology imaging agents from plasma to the CNS extracellular matrix and subsequently to the cytoplasm of neurons, where they can bind to intracellular tau inclusions. Based on these encouraging preliminary data using nonlabeled compounds, a subset of these compounds was radiolabeled for use in PET imaging of Tg mice that model tau pathology, and a radioligand that yielded the best visualization of tau lesions in these Tg mice was selected for further testing in human AD patients and NC subjects as well as patients with probable CBD. This stepwise strategy enabled us to identify and advance the most promising PET probe for the visualization and quantitative assessment of tau pathology in the CNS of living human subjects. Interestingly, another research group has recently reported development of ¹⁸F-labeled PET ligands for tau lesions mostly through assessments of binding to brain tissues, but not recombinant tau assemblies (Zhang et al., 2012; Chien et al., 2013), as in the present approach. These radioligands have been implied to produce considerably high contrasts for tau pathologies in living AD brains, and relatively long radioactive half-life of ¹⁸F would enable delivery of radioligands from a radiosynthesis sites to multiple PET facilities. [11C]PBB3 has distinct advantages over these compounds, as exemplified by affinity for diverse tau lesions, including Tg mouse tau aggregates, applicability to multimodal imaging, and induction of smaller radioactive exposure than ¹⁸F-labeled ligands.

In the present work, we clinically validated the performance of [¹¹C]PBB3 as a tau imaging agent by comparing the distribution of [¹¹C]PBB3 with that of [¹¹C]PIB in AD brains. Tau deposits in patients with moderate or severe AD are thought to be distributed extensively in the neocortical and limbic regions (classified as Braak stage V/VI) (Braak and Braak, 1991), thereby resembling localization of senile plaques, except for the predominance

of tau aggregates in the hippocampal formation. This rationalizes the use of radioactivity in the medial temporal area as an index to validate an imaging probe for tau pathology versus Aβ deposits in AD patients from prodromal to advanced stages. Furthermore, our preliminary data suggest that [11C]PBB3 may be capable of capturing the temporospatial spreading of neurofibrillary tau pathologies from the limbic system (Braak stage III/IV or earlier) to neocortical areas (Braak stage V/VI) with the progression of AD (Figure 8). A considerable subset of tau lesions at Braak stage I/II is composed of phosphorylated tau deposits barely reactive with thioflavin-S (i.e., pretangles), and NFTs are relatively low in number and are confined to the transentorhinal cortex (Braak and Braak, 1991; Braak et al., 2011). Therefore, detection of these early tau pathologies would be more difficult. Our nextstage clinical study with expanded sample size and wider range of MMSE scores is currently ongoing to pursue tau accumulation in normal controls and subjects with mild cognitive impairments and AD at diverse stages and will bring more compelling insights into the significance of tau PET imaging in early diagnosis and prediction of AD. In addition, alterations of [11C]PBB3 retention were indicated in the transition from mild to moderate AD. Loss of PET signals in the lateral temporal cortex of a patient with moderate AD (subject 6 in Figure 8) might not result from atrophy of this region, as the hippocampus of the same subject exhibited strong [11C]PBB3 binding despite marked atrophy. Possible explanations for this change include formation of extracellular NFTs and their envelopment by astrocytes in the degenerating neocortex, profoundly modifying accessibility of these NFTs to exogenous molecules (Schmidt et al., 1988). This notion would need to be examined by combined autoradiogarphic and immunohistochemical assays of different brain regions.

Being able to visualize tau deposits with [11C]PBB3 in non-AD tauopathies, such as PSP, CBD, and related disorders, is also of major importance, as suggested in the present PET data the support detectability of tau deposition in living CBD brains. As compared with NFTs and neuropil threads in AD, abundant tau deposits are largely confined to specific neuroanatomical locations of the CNS in tau-positive, plaque-negative illnesses, as exemplified by PSP and CBD (Dickson et al., 2011), but the homogenous and low-level background signals of [11C]PBB3 in brain parenchyma indicate the possibility of detecting tau lesions in these disorders. Following such in vivo assessments, a postmortem neuropathological evaluation of scanned subjects would be required as a reference standard for PET assays of non-AD tau pathologies.

[11C]PIB-positive plaque formation nearly plateaus prior to the progression of brain atrophy in AD (Engler et al., 2006), but tau abnormalities may bridge the chasm between Aβ fibrillogenesis and neuronal death. Consistent with this notion, our PET/MRI data indicate that the deposition of tau inclusions as visualized by the intense [11C]PBB3 labeling but lacking overt [11C]PIB binding is closely associated with a local volume reduction in the hippocampal formation. Indeed, our pilot clinical PET study demonstrated that localized accumulation of [11C]PBB3 in the medial temporal region of AD patients was accompanied by marked hippocampal atrophy (Figure 7B). Notably, [11C]PBB3-PET signals were substantially increased, notwithstanding the atrophy-related partial volume effects on PET images, and this



observation may support the contribution of tau fibrils to toxic neuronal death in AD. However, these data do not immediately imply neurotoxicities of [¹¹C]PBB3-reactive tau fibrils, in light of MRI-detectable neurodegeneration uncoupled with [¹¹C]PBB3 retention in the hippocampus of PS19 mice. In the hippocampal formation of AD patients, neurons bearing NFTs that resemble those in the PS19 hippocampus may drive neurodegeneration similar to that observed in either the PS19 hippocampus or brain stem, and this issue could be addressed in future studies using [¹¹C]PBB3-PET and MRI in diverse mouse models, including PS19 and rTg4510 mice, and human subjects.

Our analyses of multiple \$\beta\$ sheet ligands illustrated electrochemical and/or conformational diversities of \beta-pleated sheets among amyloid aggregates, producing a selectivity of these compounds for a certain spectrum of fibrillar pathologies (Figures 1 and S1). Lipophilicities of the β sheet ligands could determine their reactivity with noncored plagues, as noted among the PBBs studied here (Figure 1), although the molecular properties underlying this variation are yet to be elucidated. Meanwhile, we noted that all β sheet ligands tested in the present study were reactive with dense core plaques regardless of their lipophilicities. This may affect in vivo PET signals, particularly in AD brain areas with abundant cored plaques, such as the precuneus. However, our combined autoradiographic and histochemical assessments indicated that [11C]PBB3 bound to dense core plaques accounts for less than 10% of total specific radioligand binding in these areas, and this percentage in fact includes binding to tau fibrils in plaque neurites in addition to Aß amyloid core. A second possibility to account for the diversity of ligand reactivity to tau lesions may arise from the packing distance between two juxtaposed β sheets in tau filaments and is discussed in the Supplemental Discussion.

Notably, selectivity of [11C]PBB3 for tau versus aggregates may depend on free radioligand concentration in the brain. Our autoradiographic binding assays suggested that affinity of [11C]PBB3 for NFTs is 40- to 50-fold higher than senile plaques, but binding components on tau fibrils may be more readily saturated by this radioligand than those on AB fibrils. [11C]PBB3-PET data in humans indicated that uptake of this radioligand into the brain is less than one-third of [11C]PIB uptake and that free radioligand concentration in the brain at a pseudoequilibrium state is approximately 0.2 nM or lower. In this range of concentration, [11C]PBB3 could preferentially interact with high-affinity binding components formed by tau assemblies. An excessive amount of radioligand in the brain would result in saturation of radioligand binding to tau lesions and increased binding to low-affinity, high-capacity binding components in AB plaques, and such overload of free radioligand is more likely in regions with less abundant tau pathologies. This could be even more critical in capturing early tau pathologies that originate in the hippocampal formation and may require technical improvements and methodological refinements, including high-resolution imaging, correction for motions of subjects during scans, and robust definition of VOIs on the atrophic hippocampus.

Although nonspecific [¹¹C]PBB3-PET signals in control human subjects were generally low, radioligand retention in dural venous sinuses was noticeable in all scanned individuals.

Possible mechanisms that underlie this property are discussed in the Supplemental Discussion.

The present work has also implied the potential utility of multimodal imaging systems for translational development of therapeutic agents that counteract tau fibrillogenesis. Optical imaging with a near-infrared fluorescent probe, such as PBB5, could provide the least invasive technique to assess tau accumulation in living mouse models. As demonstrated by our in vitro and ex vivo fluorescence labeling, all PBBs share a similarity in terms of their reactivity with tau aggregates. Hence, PBB5 optics may be applicable to early screening of therapeutic agents that suppress tau deposition, and the data on abundance of tau lesions obtained by this approach may be translatable to advanced stages of assessments using [11C]PBB3-PET in animal models and humans. By contrast, pharmacokinetic properties of PBB5 (Figure S5) were found to be distinct from those of electrically neutral PBBs, including PBB2 and PBB3. These considerations would be of importance in developing and using fluorescent ligands applicable to optical and PET imaging.

To conclude, our class of multimodal imaging agents offers the possibility of visual investigations of fibrillary tau pathologies at subcellular, cellular, and regional levels. These assay systems are potentially powerful tools for the longitudinal evaluation of anti-tau treatments (Marx, 2007), as a single probe may facilitate a seamless, bidirectional translation between preclinical and clinical insights. PET tracers would also serve a more immediate therapeutic purpose by enabling the assessment of the effects of anti-A β and anti-tau therapies on tau pathologies in living AD patients.

EXPERIMENTAL PROCEDURES

Compounds and Reagents

PBB1 (Wako Pure Chemical Industries), PBB2 (ABX), PBB3 (Nard Institute), PBB4 (ABX), mPBB5 (Nard Institute), desmethyl precursor of [11C]PBB2 (2-[4-(4-aminophenyl)buta-1,3-dienyl]benzothiazol-6-ol; Nard Institute), desmethyl precursor of [11C]PBB3 protected with a silyl group (5-[4-(6-tert-butyl-dimethylsilyloxy-benzothiazol-2-yl)buta-1,3-dienyl]pyridine-2-amine; Nard Institute), desmethyl precursor of [11C]mPBB5 (2-[4-(4-dimethylaminophenyl) buta-1,3-dienyl]-3-ethyl-6-hydroxybenzothiazol-3-ium; Nard Institute), and 2-[8-(4-dimethylaminophenyl)octa-1,3,5,7-tetraenyl]-3-ethylbenzothiazol-3-ium (DM-POTEB; Nard Institute) were custom synthesized. Information on other chemicals is provided in the Supplemental Experimental Procedures. ClogP for each compound was calculated using ACD Chemsketch logP software (Advanced Chemistry Development).

Animal Models

Tg mice heterozygous for human T34 (4-repeat tau isoform with 1 N-terminal insert) with FTDP-17 P301S mutation driven by mouse prion protein promoter, also referred to as PS19 mice (Yoshiyama et al., 2007), were bred and kept on a C57BL/6 background. All mice studied here were maintained and handled in accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals and our institutional guidelines. Protocols for the present animal experiments were approved by the Animal Ethics Committees of the National Institute of Radiological Sciences.

Postmortem Brain Tissues

Procedures for preparation of human and mouse brain sections are given in the Supplemental Experimental Procedures.

In Vitro and Ex Vivo Fluorescence Microscopy

Six micrometer paraffin sections generated from patient brains and 20 μm frozen sections of mouse brains were stained with $10^{-3}\%~\beta$ sheet ligands

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dissolved in 50% ethanol for 1 hr at room temperature. Images of the fluorescence signals from these compounds were captured by nonlaser (BZ-9000; Keyence Japan) and confocal laser scanning (FV-1000; Olympus) microscopes. In the confocal imaging, excitation/emission wavelengths (nm) were optimized for each compound as follows: 405/420-520 (PBB3, FSB, PIB, BF-227, BF-158, FDDNP, thioflavin-S), 488/520-580 (PBB2, PBB4), 515/ 530-630 (PBB1, curcumin), and 635/645-720 (PBB5, BF-189, DM-POTEB). Subsequently, the tested samples and adjacent sections probed serially with each ligand were autoclaved for antigen retrieval, immunostained with the anti-tau monoclonal antibody AT8 that is specific for tau phosphorylated at Ser 202 and Thr 205 (Endogen), as well as a polyclonal antibody against AβN3(pE), and inspected using the microscopes noted above. For ex vivo imaging, PS19 and non-Tg WT at 10-12 months of age were anesthetized with 1.5% (v/v) isoflurane and were given 1 mg/kg PBB1-4, 0.1 mg/kg PBB5, or 10 mg/kg FSB by syringe via tail vein. The animals were killed by decapitation at 60 min after tracer administration. Brain and spinal cord were harvested and cut into 10-µm-thick sections on a cryostat (HM560). The sections were imaged using microscopes as in the in vitro assays and were labeled with either FSB or AT8, followed by microscopic re-examination.

Ex Vivo and In Vivo Multiphoton Imaging

Experimental procedures are given in the Supplemental Experimental Procedures.

In Vivo and Ex Vivo Pulsed Laser Scanning Imaging

Noninvasive scans of isoflurane-anesthetized non-Tg WT and tau Tg mice at 12 months of age were performed using a small animal-dedicated optical imager (eXplore Optix; ART). Scan protocols are given in the Supplemental Experimental Procedures.

Radiosynthesis of [11C]PBB2

Experimental procedures are given in the Supplemental Experimental Procedures,

Radiosynthesis of [11C]PBB3

[11C]Methyl iodide was produced and transferred into 300 μl of dimethyl sulphoxide (DMSO) containing 1.5-2 mg of tert-butyldimethylsilyl desmethyl precursor and 10 mg of potassium hydroxide at room temperature. The reaction mixture was heated to 125°C and maintained for 5 min. After cooling the reaction vessel, 5 mg of tetra-n-butylammonium fluoride hydrate in 600 µl of water was added to the mixture to delete the protecting group, and then 500 μl of HPLC solvent was added to the reaction vessel. The radioactive mixture was transferred into a reservoir for HPLC purification (CAPCELL PAK C18 column, 10×250 mm; acetonitrile/50 mM ammonium formate = 4/6, 6 ml/min). The fraction corresponding to [11C]PBB3 was collected in a flask containing 100 μ l of 25% ascorbic acid solution and 75 μ l of Tween 80 in 300 μ l of ethanol and was evaporated to dryness under a vacuum. The residue was dissolved in 10 ml of saline (pH 7.4) to obtain [11C]PBB3 (970-1,990 GBq at the end of synthesis [EOS]) as an injectable solution. The final formulated product was radiochemically pure (≥95%) as detected by analytic HPLC (CAPCELL PAK C₁₈ column, 4.6 × 250 mm; acetonitrile/50 mM ammonium formate = 4/6, 2 ml/min). The specific activity of [11C]PBB3 at EOS was 37-121 GBg/µmol, and [11C]PBB3 maintained its radioactive purity exceeding 90% over 3 hr after formulation.

Radiosynthesis of [11C]mPBB5

Experimental procedures are given as Supplemental Experimental Procedures.

Radiosynthesis of [11C]PIB

Radiolabeling of PIB was performed as described elsewhere (Maeda et al., 2011). The specific activity of [11 C]PIB at EOS was 50–110 GBq/ μ mol.

In Vitro and Ex Vivo Autoradiography

Experimental procedures are given in the Supplemental Experimental Procedures.

In Vivo PET Imaging of Mice

PET scans were performed using a microPET Focus 220 animal scanner (Siemens Medical Solutions) immediately after intravenous injection of [11 C]PBB2 (28.3 \pm 10.3 MBq), [11 C]PBB3 (29.7 \pm 9.3 MBq), or [11 C]mPBB5 (32.8 \pm 5.9 MBq). Detailed procedures are provided in the Supplemental Experimental Procedures.

In Vivo PET Imaging of Humans

Three cognitively normal control subjects (64, 72, and 75 years of age; mean age, 70.3 years) and three AD patients (64, 75 and 77 years of age; mean age, 72 years) were recruited to the present work (Figure 8). Additional information on these subjects is given in the Supplemental Experimental Procedures. The current clinical study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences. Written informed consent was obtained from the subjects or their family members. PET assays were conducted with a Siemens ECAT EXACT HR+ scanner (CTI PET Systems). Detailed PET scan protocols are provided in the Supplemental Experimental Procedures. A fraction of radioactivity corresponding to unmetabolized [11C]PBB3 in plasma at 3, 10, 20, 30, and 60 min was determined by HPLC (Waters mBondapak C18 column, 7.8 x 300 mm; acetonitrile/ammonium formate mobile phase with gradient elution = 40/60, 52/48, 80/20, 80/20, 40/60, and 40/60 at 0, 6, 7, 8, 9, and 15 min, respectively; flow rate, 6 ml/min) as described elsewhere (Suzuki et al., 1999). The radiotracer injection and following scans and plasma assays were conducted in a dimly lit condition to avoid photoracemization of the chemicals.

Individual MRI data were coregistered to the PET images using PMOD software (PMOD Technologies). Volumes of interest (VOIs) were drawn on coregistered MR images and were transferred to the PET images, Procedures of image analyses are provided in the Supplemental Experimental Procedures.

We additionally carried out PET scans of a patient who was clinically diagnosed as having corticobasal syndrome, as described in the Supplemental Experimental Procedures.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, nine figures, and one table and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2013.07.037.

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EXHIBIT 80

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Alzheimer's diagnosis may gain from PET imaging of tau proteins

September 20, 2013 | By Mark Hollmer

An international group of researchers from Japan and the U.S. say they've developed a way to use PET imaging to diagnose <u>Alzheimer's</u> in a living person and then track the disease's advance. The key: an imaging agent drawn to the buildup of tau protein in the brain.

Forbes, the *BBC* and other news outlets picked up on this major advance, which, if supported by future research, could improve how patients are both diagnosed and treated for Alzheimer's. The journal *Neuron* carries the full study and its findings.

Right now, the only way to definitively diagnose Alzheimer's is through an autopsy. A number of companies are advancing imaging agents that would help, in theory, to diagnose the disease in living patients. Navidea (\$NAVB) is underway with a Phase III trial of an imaging agent that can detect beta-amyloid deposits in the brain--the compound can be a telltale sign of Alzheimer's. GE Healthcare also has an investigative imaging agent that tracks beta-amyloid, and it has done well in Phase III. Both trigger vivid images through PET scans.

As *Forbes* explains, this new study differed because it relied on a fluorescent material drawn to tau protein, thought to be another sign of Alzheimer's or budding dementia. The substance crossed the blood brain barrier and worked in both mice and several human patients. And as the *BBC* notes, those tags, combined with positron emission tomography, helped build a three-dimensional image of tau buildup in the brain that clinicians haven't had before.

These are early results, of course. But if further research can duplicate these findings, then doctors get a new way to potentially track and diagnose the disease. The advance could also give researchers a tool to test Alzheimer's drugs by tracking how the tau protein buildup responds to a given treatment through detailed PET scans. What's more, detailed imaging could lead to earlier diagnosis and treatment, which doctors believe may be the best way to slow Alzheimer's advance.

- here's the *Forbes* story
- check out the BBC's take
- here's the journal abstract

Related Articles:

Navidea keys up Alzheimer's Dx agent for Phase III

GE touts promising PhIII for Alzheimer's imaging agent

GE Healthcare joins Australian government on Alzheimer's Dx study

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Source URL: http://www.fiercediagnostics.com/story/alzheimers-diagnosis-may-gain-pet-imaging-tau-proteins/2013-09-20

EXHIBIT 81



SCIENTIFIC COMMENTARIES Time for tau

It is almost exactly 10 years since the first report of a PET ligand that specifically bound to a pathological protein in the brain was published (Klunk et al., 2004). This tracer, ¹¹C-Pittsburgh compound B (PIB), detected fibrillar aggregated forms of amyloid-β, the major constituent of the Alzheimer's disease plaque and, according to many, the initiating event in Alzheimer's disease pathogenesis. This report was soon followed by several amyloid imaging tracers that were radiolabelled with the longer half-life positronemitting nuclide ¹⁸F, opening the door to commercial manufacture and clinical application. Several of these tracers are now approved by worldwide regulatory agencies including the US Food and Drug Administration and the European Medicines Agency, although reimbursement for clinical use remains problematic. In this issue of Brain, Okamura and colleagues report the first human PET studies with a new tracer for tau, ¹⁸F-THK5105, and reveal that retention of this tracer correlates with dementia severity and brain atrophy in Alzheimer's disease (Okamura et al., 2014).

Because it is difficult to develop, test and validate a new PET imaging agent, it may have seemed overly optimistic 10 years ago to conclude that a new era in human brain imaging had begun, but it had. The latest developments are a series of PET tracers that bind to the microtubule-associated protein tau that is aggregated as neurofibrillary tangles in Alzheimer's disease. Tau-related diseases also include the group of tauopathies often referred to as frontotemporal lobar degenerations, and the highly publicized chronic traumatic encephalopathy. Tau would seem to be a difficult target for PET imaging: it may be intracellular thus requiring tracer passage across both the blood-brain barrier and cell membranes; it is found in the brain at lower concentrations than amyloid-β; and it is characterized by different isoforms reflecting alternative splicing with either three (3R) or four (4R) repeated microtubule binding domains. The first PET tau imaging agent to be reported, ¹⁸F-FDDNP, was not specific for tau and showed relatively low uptake. However, in the past few years, three research groups have investigated separate molecular structures resulting in three series of compounds that are promising taubinding PET tracers. One of these, 11C-PBB3 (Maruyama et al., 2013), has shown in vitro binding to tau in the form of neurofibrillary tangles, neuropil threads and plaque neurites in Alzheimer's disease brain tissue, and also in vitro binding to tau inclusions in tissue from patients with Pick's disease (a 3R tauopathy), or progressive supranuclear palsy and corticobasal degeneration (4R tauopathies). PET studies showed hippocampal uptake in

cognitively normal older people, and extensive cortical binding in patients with Alzheimer's disease that appeared largely consistent with the pathological staging proposed by Braak and Braak (1991). Another series of compounds includes the ¹⁸F-labelled T807 and T808 (Chien et al., 2013, 2014); these compounds both demonstrate tau binding to Alzheimer's disease brain tissue without labelling amyloid-β. They show good in vivo brain penetration in humans and patterns of retention on PET scans that again are consistent with Braak staging.

The third group of ¹⁸F-labelled compounds comprises the 'THK' series developed at Tohoku University. The first of this series, ¹⁸F-THK523, was reported by Fodero-Tavoletti *et al*. (2011), and although tissue studies indicated good selectivity for tau over amyloid-β, subsequent human PET experiments showed low cortical binding compared to binding in white matter, making signal detection difficult. Okamura and colleagues now report the first human PET studies of the related compound 18F-THK5105 (Okamura et al., 2014). They studied eight patients with Alzheimer's disease and eight older control subjects with 18F-THK5105 and ¹¹C-PIB. ¹⁸F-THK5105 data acquired over 2 h showed that tracer activity in the cerebellar cortex washed out similarly in patients and control subjects, whereas tracer retention occurred in the temporal lobe in patients with Alzheimer's disease. By 90 min post-injection, ratios in cortex to cerebellum averaged 1.32 in the inferior temporal lobe of patients (the neocortical region with highest retention) compared with 1.09 in control subjects. Although other cortical regions generally showed higher retention in patients than controls, the highest brain signal was seen in pons, and this was similar in both patients and control subjects. Other subcortical brain regions showing high uptake included putamen and white matter, which did not differ between patients and control subjects. In controls, tracer retention in medial temporal regions was higher than in neocortex, suggesting the presence of medial temporal lobe neurofibrillary tangles, a common finding in ageing. 11C-PIB uptake revealed a very different pattern, with highest uptake in precuneus and frontal cortex; uptake of the two tracers was not statistically correlated. In addition, associations were found between ¹⁸F-THK5105 retention and both cognitive and magnetic resonance volumetric measures that were not seen with ¹¹C-PIB.

These data are very supportive of the use of ¹⁸F-THK5105 in the study of Alzheimer's disease, with a number of important potential applications. Okamura et al. (2014) note that Cascast822022nd-D0600nehit: 00331133165801-1Bage1c8840/0600ate Pitent 08/0922019

¹⁸F-THK5105 retention in the inferior temporal cortex showed no overlap between patients and control subjects, suggesting that tau imaging could be diagnostically useful, although the samples are still quite small. Reports that the related compound THK523 did not bind to tau deposited in the tauopathies of corticobasal degeneration, progressive supranuclear palsy, and Pick's disease (Fodero-Tavoletti et al., 2014) may be good news if we are looking for a disease-specific biomarker, but bad news if we are looking for a biomarker to image frontotemporal lobar degeneration syndromes. The findings that brain ¹⁸F-THK5105 paralleled both clinical measures of severity and magnetic resonance measures of atrophy, though preliminary, are consistent with observations that post-mortem measures of neurofibrillary tangle pathology are among the best correlates of disease severity in patients with Alzheimer's disease and suggest that tau imaging could be a staging method that might also be useful in detecting response to a therapeutic agent. Recent attempts to develop PET amyloid imaging as surrogate markers of treatment efficacy have been disappointing in failing to show either a strong relationship with dementia severity or prediction of clinical therapeutic response (Salloway et al., 2014). Because tau pathology correlates with symptoms, tau imaging could be a potential surrogate outcome for any therapy that has clinical benefit and would certainly be a useful biomarker in a trial of a therapeutic agent targeted to tau itself, an especially important goal in relation to frontotemporal lobar degeneration.

Scientific Commentaries

In addition to potential applications to clinical trials, tau imaging will be of major benefit for understanding the pathological progression of Alzheimer's disease and differentiating it from normal ageing. Current models of Alzheimer's disease are problematic in many respects, one of which is the difficulty in defining the relative importance of neurodegeneration as opposed to amyloid- β deposition. Although early models of biomarker change in Alzheimer's disease posited that amyloid-β was an initiating event, evidence of neurodegeneration in the absence of amyloid-β has resulted in a pathological framework that admits the possibility of independent and early tauopathy in Alzheimer's disease (Jack et al., 2013). The suggestion that all of the tau imaging agents are retained in the medial temporal lobes of older control subjects offers the promise that the relationship between medial temporal tau and neocortical amyloid-β can be disentangled, as well as the relationships between both of these proteins and brain atrophy, hypometabolism and cognition.

We now have at least three distinct ligands for human tau imaging. PET imaging of neurodegenerative diseases is rapidly evolving and there will undoubtedly be new tau imaging agents on the way, along with additional agents for other proteins such as α -synuclein. In fact, Okamura *et al.* (2014) note that they have developed another related compound, ¹⁸F-THK5117, which has more favourable pharmacokinetic and binding properties. There are no data for comparison of the THK series compounds with ¹⁸F-T807 and ¹¹C-PBB3, although the ¹¹C label of PBB3 will limit its use to institutions with PET radiochemistry programs unless an ¹⁸F label can be developed. Which of these compounds is 'best' is a complex determination that will have to be defined by the

intended use and additional data that accrue in this rapidly developing field. No PET ligand is perfect, and these tau ligands are likely to differ by specificity (do they bind to different forms of tau and to non-tau targets?), sensitivity (how much tau signal can be detected compared to non-specific background binding?), pharmacokinetics (is brain penetration high and steady state achieved early enough to yield good images?) and other factors. The implications for understanding Alzheimer's disease and developing effective treatments are important, and as we learn more about the behaviour of different ligands we may open up new avenues to the study of non-Alzheimer's disease tauopathies and chronic traumatic encephalopathy. The pace of scientific discovery is accelerating and the end result will be more tools and more information that should result in more effective treatments.

Brain 2014: 137; 1570-1578 | 1571

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EXHIBIT 82

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McGRATH: Illinois Eye Institute project aims to identify CTE in the living



Updated: June 14, 2014 4:39PM

David Diaz knows he probably should have told someone about the double vision he experienced near the end of his world-class boxing career, but the disclosure would have cost him the thing that defined him and enabled him to provide for his family.

Fighters fight, and Diaz — a U.S. Olympian at 20 in 1996 and a crowd-pleasing world lightweight champion 10 years later — was a fighter's fighter.

"It was worst when I looked at somebody straight-on," he recalled. "In the ring, you're always moving your head, so I could adapt."

Diaz spent two years and four fights trying to regain the title he lost to Manny Pacquiao in a brutal ninth-round stoppage that showed "PacMan" at the peak of his relentless powers and left Diaz looking as though he had been in a knife fight. He decided he'd had enough and retired in 2011, after a sneaky right hand from Philadelphia prospect Hank Lundy sliced open his right eyebrow and drew a river of blood from the worst cut of his 41-bout pro career.

"I didn't see it coming," Diaz said.

A boxer who can't see punches coming had best seek a new line of work. Diaz also wanted to be a husband to his wife, Tonya, and a father to their boys, David, Elias and Silas.

A consultation with Dr. Robert Steinmetz led to corrective treatment for Diaz's double vision. Steinmetz, a Chicago optometrist and former college baseball player whose wife, Nicole, was a Golden Gloves boxing champion, also persuaded Diaz to participate in a research project the Illinois Eye Institute is conducting to examine whether irregularities in the vision, movements and retina/optic nerve structure in the eyes of contact-sport participants might be a marker for the tau protein that causes chronic traumatic encephalopathy (CTE) in concussed athletes.

CTE, brought on by multiple concussions, accelerates deterioration of the brain and has been cited as a factor in the deaths of several high-profile former football players, including Pittsburgh Steelers great Mike Webster and former Bears safety Dave Duerson.

"One thing that's known about CTE is it's related to the number of times you get hit in the head," said Dr. Leonard Messner, who is directing the project as executive director of the institute. "A concussion is a metabolic change within the brain, more of a biomechanical injury than structural. Eighty to 85 percent of them go unreported."

With that in mind, Messner is working with the Chicago Concussion Coalition to standardize screening procedures so concussed athletes are identified more readily and removed from harm's way. They're part of a National Hit Count Initiative designed to track how often athletes are exposed to potentially damaging collisions. And they have persuaded the Illinois High School Association to ban full-contact football drills during the offseason.

"The biggest risk factor in sustaining a concussion is having had one previously," Messner said, "and 'return to play' guidelines are purely speculative."

The Illinois project is affiliated with the Sports Legacy Institute, the Boston University-based group that has pioneered CTE research through the work of neurosurgeons Ann McKee and Robert Cantu and the tireless awareness-raising of *Head Games* author Chris Nowinski, a college football star/professional wrestler/concussion victim.

On Wednesday at the Union League Club, the Sports Legacy Institute will honor former Bears quarterback Jim McMahon for his courage in coming forward as a possible CTE case. McMahon has acknowledged experiencing memory loss, severe headaches, blurred vision and other symptoms of post-concussion syndrome.

To date, the only method of identifying CTE is through post-mortem examination of the brains of suspected victims. Researchers are

6/17/2014

working to detect its presence in the living, before the deterioration of the brain begins.

Dr. Messner's group has tested more than 30 former football players, boxers and hockey players.

"It's a macho thing with boxers to say they've never been knocked out, so they'll tell us they've never had a concussion," Dr. Steinmetz said. "But you don't have to be knocked out to have a concussion."

Diaz knows.

"I've had multiple," he said.

And though his eye-test results were in the "normal" range, he limits his boxing activity to working with a youth group in Cicero.

"I hold the mitts for them, teach them footwork," he said. "They all want to spar, but I won't get in the ring with them. If I did, I might be tempted, start thinking, 'I can still do this.' But I won't. Not many of us walk away clean. I want to be there for my kids."

UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated,

Plaintiffs,

v.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cy-00029-AB

DECLARATION OF ROBERT A. STERN, PH.D.

Robert A. Stern, Ph.D., affirms under penalty of perjury the truth of the following facts:

- 1. I am a Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology at Boston University School of Medicine. My complete *curriculum vitae* is attached at Tab A, and I highlight here some of my experience, research, and qualifications relevant to the opinions expressed below.
- 2. I am a licensed Clinical Psychologist (Massachusetts License number 7238), with a specialty in Clinical Neuropsychology. I have been licensed as a Clinical Psychologist since 1990 and have been a Registrant of the National Register of Health Service Providers in Psychology since 1992. During that time, I was Director of the Memory and Cognitive Assessment Program at Rhode Island Hospital.
- 3. Prior to that, I had been Assistant Professor of Psychiatry at the University of North Carolina (UNC) School of Medicine at Chapel Hill, North Carolina, where I had been on the faculty since 1990. During that time, I was Director of the Neurobehavioral Assessment Laboratory as well as the Associate Director of the federally-funded Mental Health Clinical Research Center.

- 4. I received my Ph.D. in Clinical Psychology from the University of Rhode Island (dissertation titled, "Mood Disorders following Stroke"), completed my pre-doctoral internship training in Clinical Neuropsychology at the Boston Veterans Administration Medical Center, and completed my post-doctoral fellowship research and clinical training in both Neuropsychology and Psychoneuroendocrinology at UNC School of Medicine.
- 5. I am a Fellow of both the American Neuropsychiatric Association and the National Academy of Neuropsychology. I sit on the editorial boards of several leading medical and scientific journals, and on the grant review committees of several international, national (e.g., National Institutes of Health, NIH), and foundation funding agencies. I am a member of the medical and scientific advisory boards of the MA/NH Chapter of the Alzheimer's Association, the National Grave's Disease Foundation, and Sports Legacy Institute, and am also a member of the Mackey White Traumatic Brain Injury Committee of the National Football League Players Association.
- 6. Throughout my 25 year career, I have taught medical students and young physicians (neurology residents, psychiatry residents, and geriatrics fellows) through courses and required training seminars in the areas of neurobehavioral mental status examination, brain-behavior relationships, assessment of dementia, the diagnosis and treatment of Alzheimer's disease and related disorders, chronic traumatic encephalopathy (CTE), and similar areas of their formal training.
- 7. I have been a lecturer in, and a course director of, several continuing medical education (CME) courses for physicians, both locally and nationally.
- 8. I have been an invited lecturer (and keynote lecturer) for numerous national and international medical and scientific meetings, speaking primarily in the area of Alzheimer's disease, CTE, and issues pertaining to the evaluation and assessment of the cognitive, mood, and behavioral aspects of neurodegenerative disease.
- 9. I have also been the mentor for numerous undergraduate students, graduate students (Ph.D. students, master's degree students, medical students, M.D./Ph.D. students), and post-doctoral fellows, and have been the primary mentor of many masters theses and Ph.D. dissertations.

- 10. One of my areas of specialization and expertise includes the assessment and evaluation of neurocognitive functioning. I have published extensively in this area and have also been the primary author of several widely used, standardized neuropsychological tests, including the 33 tests of memory, language, attention, executive functioning, and spatial skills that make up the *Neuropsychological Assessment Battery* (NAB).
- 11. I have directed predoctoral and postdoctoral training programs in Clinical Neuropsychology, and have served as the mentor for numerous trainees learning to become neuropsychologists.
- 12. I have given invited lectures at the New York Academy of Sciences and for the Coalition Against Major Diseases in Washington, DC, providing guidance and education to members of the Federal Drug Administration, senior thought leaders in the pharmaceutical industry, and fellow scientists about neurocognitive assessment issues for Alzheimer's disease clinical trials.
- 13. As a clinical neuropsychologist with a specialty in the evaluation and diagnosis of neurodegenerative diseases, I conduct clinical examinations of patients referred to me by neurologists, geriatricians, psychiatrists, primary care physicians, and others, for diagnostic impressions and treatment recommendations.
- 14. My clinical neuroscience research focuses on the risk factors for, and the diagnosis and treatment of, neurodegenerative diseases and other causes of cognitive, mood, and behavior change in aging. Currently, I am the Clinical Core Director of the Boston University (BU) Alzheimer's Disease Center (ADC), one of 27 research centers across the country funded by the National Institute on Aging (NIA) of the National Institutes of Health (NIH). In this capacity, I oversee all clinical research (i.e., research conducted on living humans) pertaining to Alzheimer's disease, including studies aimed at the early diagnosis of Alzheimer's disease, genetics, and clinical trials of new medicines to prevent or treat Alzheimer's disease.
- 15. As part of my role as Clinical Core Director of the BU ADC, I oversee a weekly multidisciplinary diagnostic consensus conference involving neurologists, neuropsychologists, psychiatrists, geriatricians, and others, at which we review the histories, medical tests (including neuroimaging), clinical evaluations, and neuropsychological test performance of research participants and determine the specific

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diagnosis (e.g., Alzheimer's disease dementia, Frontotemporal Dementia, Vascular Dementia, Mild Cognitive Impairment, Chronic Traumatic Encephalopathy) of each individual.

- 16. My other area of currently NIH-funded research includes the cognitive effects of chemotherapy in older breast cancer patients; my co-principal investigators on this grant are from the Georgetown Lombardi Comprehensive Cancer Center and the Memorial Sloan Kettering Cancer Center.
- 17. Since 2008, my primary area of research has been the long-term consequences of repetitive brain trauma in athletes (see listing of publications below). I was a co-founder of the BU Center for the Study of Traumatic Encephalopathy (CSTE, now "CTE Center") and I serve as the leader of clinical research for the CTE Center. I have received R01 grant funding from NIH (the first grant ever funded by NIH for the study of CTE) to develop biomarkers for the *in vivo* (i.e., during life) detection and diagnosis of CTE.
- 18. This project, called the Diagnosis and Evaluation of Traumatic Encephalopathy using Clinical Tests (DETECT) study, involves the examination of 100 former professional football players (selected based on positions played, their overall exposure to repetitive brain trauma using data from helmet sensors, and existing clinical symptoms) and 50 same-age non-contact sport elite athletes. All research participants (approximately 100 to date) undergo extensive brain scans, lumbar punctures (to measure proteins in cerebrospinal fluid), electrophysiological studies, blood tests (e.g., for genetic studies and other state-of-the-art biomarkers), and indepth neurological, neuropsychological, and psychiatric evaluations. For this project, I oversee a talented multidisciplinary group of investigators with specialties in neurology, psychiatry, neuroimaging, radiology, genetics, and biostatistics.
- 19. In addition, I have recently received Department of Defense funding (with my co-principal investigator, Dr. Martha Shenton from Harvard Medical School) to examine a new Positron Emission Tomography (PET) ligand (T807) that is specific to the abnormal forms of tau protein found in CTE.
- 20. Relatedly, I am principal investigator of a new study funded by Avid Radiopharmaceuticals to examine that same PET ligand (and another PET ligand for the amyloid protein found in AD) in participants in the DETECT study. I view these two studies of the T807 PET test as the most important investigations in the field of CTE research.

- 21. I am also the principal investigator of a telephone- and web-based longitudinal study (Longitudinal Evaluation to Gather Evidence of Neurodegenerative Disease; LEGEND) of over 600 adult former and current athletes across all sports and levels of play (including collegiate) to assess risk factors (including brain trauma exposure, genetics, and lifestyle) and clinical course of CTE and other short-term and long-term consequences of repetitive brain trauma.
- 22. I have conducted over 100 in-depth retrospective clinical interviews with the next-of-kin of the deceased athletes (and others) in Dr. Ann McKee's VA-BU-SLI brain bank. For these cases, I also reviewed all of the available medical records. I currently am a co-investigator of Dr. McKee's NIH-funded U01 project aimed at defining the neuropathology of CTE. For that study, I am a member of the multidisciplinary group of clinicians and scientists who review the clinical history of every new case in the brain bank in order to determine the clinical diagnosis prior to being provided with the neuropathological diagnosis for the case.
- 23. Based on these experiences, I am confident that I have the same or more experience than any other scientist or clinician in the world examining the clinical history and presentation of athletes (including former NFL players) with post-mortem diagnosed CTE, through detailed interviews and discussions with the decedents' family members, friends, significant others, and physicians.
- 24. Based on the data gathered through these interviews and medical records, I have published (as first or second author) the largest case series of the clinical presentation of neuropathologically-confirmed CTE (Stern et al., 2013; McKee, Stern, et al., 2013).
- 25. I am the senior author of an important new journal article (Montenigro et al., 2014) that describes the first clinical diagnostic criteria for CTE and Traumatic Encephalopathy Syndrome (TES), based, in part, on the information gathered from the post-mortem family interviews of over 75 neuropathologically confirmed cases of CTE, and on an extensive review of the world's literature on CTE and "dementia pugilistica."
- 26. Our group of researchers at BU has been playing a central role nationally and internationally in the area of CTE and the long-term consequences of repetitive brain trauma, including concussions and subconcussive blows. I was the co-director of the first ever national scientific meeting on CTE and have been an invited speaker at numerous national and international conferences, including the first two workshops held

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by NIH on this topic. I have published extensively in this area of research including several empirical papers in high impact peer-reviewed scientific journals. I am the invited editor of a special series on CTE and traumatic brain injury (TBI) for the journal, *Alzheimer's Research and Therapy*. I recently testified about this issue before the US Senate Special Committee on Aging.

- 27. My experience has included extensive clinical- and research-based interviews with former professional football players and their relatives regarding the mid to late life changes in cognition, behavior, mood and daily functioning observed in these persons.
- 28. My statements and views included in this declaration are mine alone and do not reflect those of Boston University or any of the departments and centers with which I am involved. Specifically, they do not reflect the views of the Boston University Alzheimer's Disease Center, the Boston University CTE Center, or the Boston University Center for the Study of Traumatic Encephalopathy; nor do they reflect any of the faculty, staff, or administration associated with any of these organizations.
- 29. I have not received any financial payments for preparing this Declaration from any source, including any attorney or plaintiff in this case. Furthermore, I am not retained by, nor receive any payments from plaintiff attorneys in this case for the purpose of this case.

I. CLASS MEMBERS WHO SUFFER FROM MANY OF THE MOST DISTURBING AND DISABLING SYMPTOMS OF CTE WOULD NOT BE COMPENSATED UNDER THE SETTLEMENT

- 30. I have reviewed the Class Action Settlement Agreement as of June 25, 2014, together with its exhibits (the "Settlement"), filed in the above captioned proceeding. I have paid particular attention to Articles III through IX, and Exhibits 1, 2, and 3, of the Settlement, relating to testing and compensation of the class of retired NFL football players and their families.
- 31. The primary clinical features of CTE include impaired cognition, mood, and behavior (e.g., Stern et al., 2013). However, the Baseline Neuropsychological Test Battery set forth in Exhibit 2 of the Settlement (the "Test Battery") is focused primarily on the assessment of cognitive impairment, and excludes problems in mood and behavior in the algorithm used to define Neurocognitive Impairment Levels 1, 1.5, or 2.

- 32. The behavioral and mood disorders associated with head impacts in former professional football players are just as important, just as serious, and just as amenable to detection and diagnosis, as cognitive disorders. Individuals with neuropathologically confirmed CTE have had significant problems with mood and behavior and not just problems with cognition. In the study from my research team (Stern et al., 2013) published in the journal, Neurology, 22 of 33 deceased former athletes with neuropathologically confirmed CTE (and no other abnormal brain findings) were reported to have behavior or mood problems as their initial difficulties, prior to any cognitive impairment. Only 10 of 33 were ever diagnosed with dementia at any time prior to death. These numbers are provided not as an estimate of expected future diagnoses or as an estimate of the prevalence of dementia amongst all individuals with CTE. Rather, they are presented to underscore the findings from our group and from all other descriptions of CTE that dementia and cognitive impairment are not the only life-altering problems experienced by individuals with CTE.
- 33. Individuals with impairments in mood and behavior, but without significant cognitive impairment can still experience devastating changes in their lives. Based on my review of the medical and scientific literature and on my interviews of living research participants, informal discussions with former players and/or their family members, and formal interviews with family members of deceased former players with neuropathologically confirmed CTE, it is my scientific opinion that many former NFL players have significant changes in mood and behavior (e.g., depression, hopelessness, impulsivity, explosiveness, rage, aggression), resulting, in part, from their repetitive head impacts in the NFL, that have, in turn, led to significant financial, personal, and medical changes, including, but not limited to: the inability to maintain employment, homelessness, social isolation, domestic abuse, divorce, substance abuse, excessive gambling, poor financial decision-making, and death from accidental drug overdose or suicide.
- 34. The significant changes in mood and behavior relatively early in life can lead to significant distress for the individual with CTE as well as their family, friends, and other loved ones. I have learned about the tremendous pain and suffering the family members experienced while their loved one's life was destroyed by the progressive destruction of the brain. I have interviewed the adult children of former professional and college football and rugby players whose fathers had dramatic changes in personality, the development of

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aggressive and out-of-control behavior, and suicidal thoughts. And, I have spoken with the parents of young athletes in their 20's and 30's who impulsively took their own lives.

- 35. Several well-known former NFL players who were diagnosed neuropathologically with CTE following death did not have dementia and would not have been found impaired under the proposed Baseline Assessment Program of the Settlement (the "BAP"). For example, based on publicly available information, Junior Seau (diagnosed with CTE by a group of independent neuropathologists coordinated by the NIH), and Dave Duerson (diagnosed with CTE by Dr. McKee at BU), both died from suicide reportedly after years of significant changes in mood and behavior, including depression, hopelessness, aggression, and poor impulse control. Based on public reports of their functioning by their family members and friends, it is unlikely that their cognitive skills were impaired to the degree of meeting the criteria for Level 1.5 or Level 2 Neurocognitive Impairment. Rather, their primary symptoms involved mood and behavioral disturbance, neither of which is compensable in the Settlement. Notwithstanding important limitations and criticisms of the test battery and criteria described below, Level 1.5 and Level 2 Neurocognitive Impairment do not include any impairment in mood or behavior. Thus if either of these individuals died on July 8, 2014 or later, their families would not receive any compensation under the Settlement.
- 36. CTE is a unique neurodegenerative disease. It is not Alzheimer's disease (AD), Parkinson's disease, or ALS. All of these diseases are diagnosed through careful neuropathological examination of brain tissue following death.
- 37. AD cannot accurately be diagnosed during life, although there have been tremendous strides over the past decade in developing specific, objective biological markers (biomarkers) that improve the predictive accuracy of the diagnosis during life. These biomarkers are now used routinely in research studies and are beginning to be used in clinical settings.
- 38. CTE also cannot accurately be diagnosed during life, although there are methods being developed at this time by my research team and by others that are meant to improve our ability to do so and to distinguish CTE from AD and other brain diseases and conditions. Based on the scientific and medical literature, my own first-hand knowledge of the current state of the scientific field, and on my own research, I am

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confident that within the next five to ten years there will be highly accurate, clinically accepted, and FDA-approved methods to diagnose CTE during life. Based on my involvement in, and understanding of, current ongoing research, it is my scientific opinion that the understanding of neurodegenerative conditions and the capabilities of diagnostic tests will advance rapidly over the next 65 years.

- 39. Dementia is not an illness or disease. Dementia is a clinical syndrome diagnosed when there are cognitive symptoms that interfere with the ability to function at work or at usual activities, and the patient exhibits a decline from previous levels of functioning that is not explained by delirium or major psychiatric disorder (McKhann et al., 2011; National Institute on Aging and the Alzheimer's Association workgroup).
- 40. There are several neurodegenerative diseases that can lead to dementia. AD, CTE, and Parkinson's all are neurodegenerative diseases that can lead to dementia. These diseases begin many years or decades prior to any symptoms. When enough brain tissue is destroyed by the disease, symptoms begin to develop. When the symptoms begin, they would not be considered "dementia." When there are cognitive impairments, but not to the degree of interfering with daily functioning, the clinical syndrome of Mild Cognitive Impairment (MCI) may be diagnosed; MCI is not a disease, it is merely a clinical syndrome. It is only when these diseases progress further and the symptoms become bad enough to interfere with the ability to function independently that the individual would be diagnosed with dementia. That is, AD, CTE, and Parkinson's disease each are independent brain diseases that eventually can lead to dementia, later in the course of the disease.
- 41. The only symptoms related to CTE that are compensable (other than those that overlap with Alzheimer's disease, ALS or Parkinson's) are cognitive difficulties, and only cognitive difficulties that are severe enough that the Class Member would have significant impairments in critical aspects of daily living and independence. Several key symptoms of CTE that are identified in the scientific and medical literature and in my clinical and research experience are not compensable.
- 42. Class members who clearly have dementia but whose doctors have determined, by appropriate and currently approved medical tests, that they likely have CTE and not Alzheimer's disease as the cause of the dementia would receive substantially less compensation than Class members whose doctors do not order the

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tests to assist in the diagnosis. At this time, there are two U.S. Food and Drug Administration (FDA)-approved PET scan tests for patients being evaluated for Alzheimer's disease and dementia: Amyvid (Florbetapir F 18 injection) and Vizamyl (flutemetamol F 18 injection). The following is from an FDA Press Release dated October 25, 2013: "Many Americans are evaluated every year to determine the cause of diminishing neurologic functions, such as memory and judgment, that raise the possibility of Alzheimer's disease,' said Shaw Chen, M.D., deputy director of the Office of Drug Evaluation IV in the FDA's Center for Drug Evaluation and Research. 'Imaging drugs like Vizamyl provide physicians with important tools to help evaluate patients for AD and dementia...A negative Vizamyl scan means that there is little or no beta amyloid accumulation in the brain and the cause of the dementia is probably not due to AD."

As an exemplar, I will compare two hypothetical cases, both age 62 with the same number of qualifying seasons in the NFL. They both have had a progressive history of cognitive, behavioral, and mood symptoms and are now having difficulties carrying out daily activities. They receive the exact same test scores on the Neuropsychological Test Battery and meet the criteria for Neurocognitive Impairment 1.5. They are examined by two different neurologists. Both neurologists conduct neurological evaluations, order the blood tests, and order the same MRI scans. The findings of all these tests come back similarly negative. Both cases are diagnosed by their neurologists as having "dementia." However, Case A's neurologist diagnoses him with Alzheimer's disease. Case B's neurologist decides to order a Florbetapir (Amyvid) PET scan. That specific FDA-approved test is labeled by the FDA to be used to help rule out Alzheimer's disease in cases when the differential diagnosis may be questionable. That is, if the test is found to be negative (indicating little or no abnormal beta amyloid protein build up in the brain), the patient unlikely has Alzheimer's disease as the cause of their dementia. For Case B, because the neurologist knew that CTE was a possible cause for dementia in an individual with a history of repetitive brain trauma, the neurologist felt that the Florbetapir PET scan would be helpful in clarifying the diagnosis. The result of the scan came back negative, resulting in the neurologist determining that the patient does not have Alzheimer's disease. Case A, with a diagnosis of Alzheimer's disease as the cause of dementia, would be eligible for compensation of \$950,000 according to the Settlement's Monetary Award Grid. Case B, with a diagnosis of Probable CTE as the cause of dementia (the neurologist

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could not give a diagnosis of Alzheimer's based on the negative Florbetapir scan), would not be covered for anything other than Neurocognitive Impairment Level 1.5 and would be eligible for compensation of \$290,000. That is, two individuals with identical histories and clinical presentations would receive strikingly disparate compensation solely because of the decision of one of the neurologists to use a very appropriate, FDA-approved test to make a more accurate diagnosis (i.e., not Alzheimer's disease). The former NFL player who received that accurate diagnosis would receive \$660,000 less than the former NFL player with the imprecise/incomplete diagnosis.

II. THE BASELINE NEUROPSYCHOLOGICAL TEST BATTERY IS INAPPROPRIATE FOR THE EVALUATION OF THE CLASS MEMBERS FOR WHOM IT IS MEANT TO BE USED

- 43. The Test Battery, set forth in Exhibit 2 of the Settlement, is not appropriate for evaluating whether retired professional football players have neurodegenerative diseases such as CTE or Alzheimer's disease. Rather, it is appropriate only for the evaluation of a younger traumatic brain injury patient. The specific tests selected, and the length of the battery would not be consistent with that given by the large majority of neuropsychologists who specialize in neurodegenerative disease and who evaluate patients for Mild Cognitive Impairment and Alzheimer's disease dementia.
- 44. Based on information provided by the test publishers and by my extensive clinical experience with dementia patients, it is estimated that the Test Battery in the Settlement would take approximately five hours without any break. For patients with the level of severity required for compensation (i.e., Level 1.5 or 2 Neurocognitive Impairment), this length of testing would be excessive, would result in refusals to complete the evaluation, and would result in inaccurate results.
- 45. The Test Battery includes two measures of "Mental Health" even though the results of those tests are not included anywhere in the criteria for impairment. In addition, based on the scientific and medical literature and on my clinical and research experience, the two tests are not appropriate for the detection and diagnosis of the specific types of behavioral and mood disorders linked to a history of head impacts in former professional football players. One of these two tests, the Mini International Neuropsychiatric Interview (M.I.N.I.), is not sufficient to evaluate specific areas of impairments, such as impulsivity, rage, and aggression.

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Further, its inclusion in the battery is unnecessary because the results are not used in any way to determine compensable diagnosis. The second of these tests, the MMPI-2RF, is inappropriate for patients with dementia. Even if the results were to be used for any reason, they would likely be inaccurate or incomplete in that the test requires the patient to complete 338 yes-no questions about psychological state and personality; such a task would not be possible by the majority of patients with the severity of dementia included in the compensable diagnoses. As described above, it is my opinion that there must be an appropriate evaluation of mood and behavioral impairment as part of the BAP evaluation, and in the proposed Settlement none exists and there is no inclusion of any mood or behavioral impairment in the definitions of compensable diagnoses.

46. The Test Battery includes extensive testing for performance validity in order to assure that the Class Member's test data represent a valid reflection of the former player's optimal level of functioning, even though patients with moderate dementia have been found to perform poorly (i.e., false positives) on effort testing. Although it is appropriate to consider suboptimal effort in any neuropsychological evaluation for possible compensation, it should be noted that the only compensable findings of the evaluation are Level 1.5 and 2 Neurocognitive Impairment. These represent mild to moderate stages of dementia and require significant impairment on numerous tests in the battery. There have been several studies that indicate that recommended cut-off scores on at least one of the effort tests included in the battery (Test of Memory Malingering) are not appropriate for use in patients with dementia due to an excessive number of false positives (e.g., Bortnick et al., 2013; Teichner & Wagner, 2004). That is, because patients with dementia are so impaired cognitively, they may perform poorly on the effort test due to their actual cognitive impairment rather than poor effort or malingering. It is my scientific opinion, based on the medical and scientific literature and on my own clinical and research experience, that reliance on the effort measures included in the Neuropsychological Test Battery would unfairly deprive at least some otherwise eligible persons with measurable cognitive deficits of compensation.

III. THE HIGH THRESHOLD FOR COMPENSATION BASED ON LEVEL OF COGNITIVE IMPAIRMENT DEFINED BY THE SPECIFIC TEST FINDINGS AND ALGORITHM DETAILED IN EXHIBIT 2 OF THE SETTLEMENT WOULD DEPRIVE PERSONS WITH DOCUMENTED COGNITIVE DEFICITS OF COMPENSATION.

- 47. To be eligible for compensation under Neurocognitive Impairment Level 1.5 or 2.0, the Class Member would have to be so severely impaired in several areas of cognitive functioning that they would require assistance in many activities of daily living (in Level 1.5) or be almost fully dependent on another person for most activities of daily living, such as bathing and toileting (for Level 2.0). Specifically, the definitions of Level 1.5 Neurocognitive Impairment and Level 2 Neurocognitive impairment require that the Class Member exhibits functional impairment consistent with the criteria set forth in the National Alzheimer's Coordinating Center's (NACC) Clinical Dementia Rating (CDR) scale. For Level 1.5 Neurocognitive Impairment, the Class Member must meet criteria for CDR Category 1.0 in the areas of Community Affairs, Home & Hobbies, and Personal Care. For Level 2 Neurocognitive Impairment, the Class Member must meet criteria for CDR Category 2.0 in the areas of Community Affairs, Home & Hobbies, and Personal Care. According to the CDR, Category 1.0 would require the individual to be unable to function independently at a job, shopping, and volunteer and social groups; to have mild but definite impairment in functioning independently at home, with more difficult chores abandoned, and more complicated hobbies and interests abandoned; and would need prompting for personal care functions, such as dressing, toileting, and bathing. CDR Category 2.0 would require the individual to have no pretense of independent functioning outside home; would only have simple chores preserved; would have very restricted interests; and would require assistance in dressing, hygiene, and NACC. keeping of personal effects (Morris, 1993: https://www.alz.washington.edu/ NONMEMBER/UDS/DOCS/VER2/ivpguide.pdf).
- A8. The algorithm used in the Settlement to translate test performance into compensable Neurocognitive Impairment categories is not one that is used in any known or published set of criteria for the determination of dementia, and utilizes a threshold of impairment that would exclude many Class Members with dementia. To clarify the specific content of Exhibit 2 of the Settlement and understand the algorithm used, it is important to understand the statistical terminology used in the criteria. Neuropsychological tests are developed to result in test scores that are roughly distributed as a normal ("bell-shaped") curve. The tests are typically standardized on a large group of healthy individuals who do not have any known neurological disorder or other possible cause of cognitive impairment. That "normative group" is made up of individuals across

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different age and educational levels, as well as gender and sometimes ethnic, racial, and geographical groups. The results of the normative group's performance on the test are used to create standardized scores, such that when the test is administered to a patient (or in this case a former NFL player), that person's raw score (e.g., the number correct or the time to completion) is compared to the scores from the appropriate reference group from the normative sample. The raw score is then transformed to a standardized score that is then used to interpret the level of performance.

- 49. A T score is one of the types of standardized scores used to determine the level of performance on the test by the patient. A T score has a mean of 50 (i.e., the average score of the reference normative group is 50) and a standard deviation of 10. A standard deviation is a measure of the distribution of scores in the normative group, such that approximately 68% of the normative group scored within one standard deviation of the mean. That translates into 68% of the healthy normative group having T scores between 40 and 60. Another way to interpret this is that a T score of 40 would be equivalent to approximately the 16th percentile, i.e., only 16 percent of the "normal" healthy population would be expected to score below that level. A T score of 30 (i.e., two standard deviations below the mean) would indicate that only 2.3 percent of the healthy population would be expected to score below that level.
- 50. As described in Exhibit 2 of the Settlement, the "basic principle for defining impairment on testing is that there must be a pattern of performance that is approximately ... 1.7-1.8 standard deviations (for Level 1.5 Impairment) or 2 standard deviations (for Level 2 Impairment) below the person's expected level of premorbid functioning." (Settlement, Exhibit 2, p. 5). Using the tables provided in Exhibit 2 of the Settlement, a Class Member with Average Estimated Intellectual Functioning, for example, would be required to perform worse than 97 percent of same age peers in the published normative reference group on two or more (of six) Learning and Memory tests AND two or more (of four) Executive Function tests, in order to qualify for benefits under the Settlement. As seen in several studies comparing cognitively healthy elderly controls with patients diagnosed with moderate dementia, and often even with severe dementia, it is not common for dementia patients to score consistently more than two standard deviations below healthy controls (e.g., Caccappolo-Van Vliet et al., 2003; de Jager et al., 2003). However, the criteria used in the Settlement would require that the

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Class Member's test performance be even more impaired than what is often seen in well-diagnosed cases of moderate stage dementia.

- 51. The algorithm used to translate test performance into compensable Neurocognitive Impairment categories is arbitrary, nonstandard, and not supported by any scientific literature. There are three different tables in Exhibit 2 of the Settlement used to determine the specific levels of test performance required to meet the categories of Neurocognitive Impairment based on three different levels of "Estimated Intellectual Functioning." That is, the specific number of impaired tests per cognitive domain (e.g., 3 or more versus 2 or more) and the specific level of impairment (e.g., T Score below 35 versus below 37) is different based on whether a Class Member is determined to have Below Average, Average, or Above Average Estimated Intellectual Functioning. Although it is common practice in neuropsychological assessment to compare an individual's performance to expected premorbid levels for that individual, it is uncommon to create distinct criteria tables for levels of impairment based on a single estimate of premorbid functioning to be used across large groups of individuals. And, most importantly, for an algorithm to be used for any decision-making purpose (e.g., determination of large sums of compensation), it must be shown to be valid and reliable in the specific population for which it is being used, a process that requires extensive research. There is no mention in the description of this algorithm that it has undergone any research to determine its appropriateness for this use.
- 52. As defined in Exhibit 2 of the Settlement, Estimated Premorbid Intellectual Ability is determined by the Test of Premorbid Functioning (TOPF), which "provides three models for predicting premorbid functioning: (a) demographics only, (b) TOPF only, and (c) combined demographics and TOPF prediction equations" (Settlement Exhibit 2, p. 4).
- 53. Based on the TOPF, Class Members would be categorized into one of the following three categories of Estimated Intellectual Functioning: (1) Below Average (estimated IQ below 90); (2) Average (estimated IQ between 90 and 109); and (3) Above Average (estimated IQ above 110). A Class Member who, based solely on the TOPF predictions of premorbid functioning, is in the Below Average category would have to perform more poorly on more tests than a Class Member who is in the Average or Above Average categories. As an additional exemplar, I will compare two hypothetical cases who receive the exact same test scores on the

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Neuropsychological Test Battery with the exception of TOPF scores. Based on the TOPF, the first case would be classified as having Below Average Estimated Intellectual Functioning, whereas the second case would be classified as having Above Average Estimated Intellectual Functioning. The age of both cases is the same, as is the number of qualifying seasons in the NFL. In both cases, the two worse areas of performance are in Learning and Memory and Executive Function. Both cases had two Learning and Memory tests with T scores of 34 and one Learning and Memory test with a T score of 36; all other Learning and Memory tests had better scores (i.e., T scores above 37). Both cases also had two Executive Function tests with T scores of 35 and one Executive Function test with a T score of 36; all other Executive Function tests had better scores (i.e., T scores above 40). Therefore, with the exact same performance on the exact same tests (other than the TOPF word pronunciation test), the first case would not qualify for any compensable diagnosis, whereas the second case would qualify for financial compensation with a diagnosis of Level 1.5 Neurocognitive Impairment.

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Stamm, J.M., Robbins, C.A., McHale, L., Simkin, I., Stein, T.D., Alvarez, V., Goldstein, L.E., Budson, A.E.,

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cognitively intact, cognitively impaired, and elderly patients with dementia. Archives of Clinical

Neuropsychology, 19, 455-464.

Pursuant to 28 U.S.C. § 1746, I state under penalty of perjury that the foregoing is true and correct:

Robert A. Stern, Ph.D.

Date: October 6, 2014

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ACADEMIC TRAINING:

1980 B.A.	Wesleyan University, Middletown, CT
1984 M.A.	University of Rhode Island, Kingston, RI, Psychology
1988 Ph.D.	University of Rhode Island, Kingston, RI, Clinical Psychology (Clinical
	Neuropsychology Specialization);
1986-1987	Pre-Doctoral Internship in Clinical Neuropsychology; Mentor Edith Kaplan, Ph.D.;
	Department of Veterans Affairs Medical Center, Boston, MA

POSTDOCTORAL TRAINING:

1988-1990 Fellow in Neuropsychology and Psychoneuroendocrinology; Mentor Arthur J. Prange, Jr., MD; University of North Carolina School of Medicine, Chapel Hill, NC

ACADEMIC APPOINTMENTS:

1988-1990	Clinical Instructor of Psychiatry, University of North Carolina School of Medicine
1990-1993	Assistant Professor of Psychiatry, University of North Carolina School of Medicine
1991-1993	Clinical Assistant Professor of Speech and Hearing Sciences, University of North
	Carolina School of Medicine
1991 - 1993	Research Scientist, Brain and Development Research Center University of North
	Carolina School of Medicine
1993-1996	Assistant Professor of Psychiatry and Human Behavior, Brown Medical School
1993-1996	Assistant Professor of Clinical Neurosciences (Neurology), Brown Medical School
1994-2004	Adjunct Assistant Professor, Behavioral Neuroscience Program, Division of Graduate
	Medical Sciences, Boston University School of Medicine
1996-2003	Associate Professor of Psychiatry and Human Behavior, Brown Medical School
1996-2003	Associate Professor of Clinical Neurosciences (Neurology), Brown Medical School
1997-2004	Graduate Faculty Member, University of Rhode Island
2002-2003	Faculty Member, Brain Science Program, Brown University
2005-Present	Faculty Member, Behavioral Neuroscience Program, Division of Graduate Medical
	Sciences, Boston University School of Medicine
2005-2011	Associate Professor of Neurology, Boston University School of Medicine
2011-Present	Professor of Neurology and Neurosurgery, Boston University School of Medicine
2014-Present	Professor of Neurology, Neurosurgery, and Anatomy and Neurobiology, Boston
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HOSPITAL APPOINT	TMENTS:
1986-1988	Assistant in Neuropsychology, McLean Hospital, Belmont, MA
1990-1993	Clinical Neuropsychologist; Director, Adult Neuropsychology Laboratory; UNC
	Hospitals, Chapel Hill, NC
1993-2003	Clinical Neuropsychologist, Women's and Infants Hospital, Providence, RI
1993-2003	Clinical Neuropsychologist, Rhode Island Hospital, Providence, RI
1994-1995	Supervising Neuropsychologist, Slater Hospital, Cranston, RI
1994-2003	Director, Memory and Cognitive Assessment Program, Rhode Island Hospital,
	Providence, RI
1997-2003	Director, Neuropsychology Program; Rhode Island Hospital, Providence, RI
2004-Present	Clinical Neuropsychologist, Boston Medical Center (Boston University Neurology
	Associates), Boston, MA
2014-Present	Core Faculty Member, Boston Medical Center Injury Prevention Center
Honors:	
1980	Honors in Psychology, Wesleyan University, Middletown, CT
1980	Heidman Prize (for Community Service), Wesleyan University, Middletown, CT
1984	Psi Chi National Honor Society in Psychology
1988	Phi Kappa Phi National Honor Society
1997	Master of Arts ad eundem, Brown University, Providence, RI
1997	Independent Investigator Award, National Alliance for Research on Schizophrenia &
	Depression (NARSAD)
1999	Outstanding Teaching Award in Psychology, Brown University School of Medicine,
	Providence, RI
2001	Fellow, American Neuropsychiatric Association
2001	Fellow, National Academy of Neuropsychology
2008	National Research Award, Alzheimer's Association MA/NH Chapter
LICENSES AND CER	TIFICATION:
1990-1994	Licensed Psychologist, North Carolina License # 1560
1993-2008	Licensed Psychologist, Rhode Island # 491
1992-Present	Registrant, National Register of Health Service Providers in Psychology
1997-Present	Licensed Psychologist HSP, Massachusetts # 7238
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	ND UNIVERSITY COMMITTEES:
1994-1995	Leadership Committee, Department of Psychiatry, Rhode Island Hospital
1994-1996	Committee for the Protection of the Rights of Human Subjects (IRB), Rhode Island
1004 1007	Hospital
1994-1997	Research Committee, Department of Psychiatry and Human Behavior, Brown Medical
1005 1006	School, RI
1995-1996	IRB Executive Committee Member, Rhode Island Hospital
1995-2003	Brown University Geriatric Neuropsychiatry Research and Treatment Program, Brown
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1998-2000	Continuing Medical Education Subcommittee, Department of Psychiatry, Rhode Island
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1999-2002	Library Committee, Lifespan (Rhode Island Hospital and Miriam Hospital)
2001-2002	Training Committee, Brown University Clinical Psychology Training Consortium,
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2006-2012 Executive Committee, Alzheimer's Disease Advisory (Philanthropic) Board, Boston

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2012-present Faculty Appointment and Promotions Committee, Boston University School of Medicine

TEACHING EXPERIENCE AND RESPONSIBILITIES:

1990-1993	Member, Clinical Psychology Training Program, UNC School of Medicine
1990-1993	Regular Lecturer for Internship Seminar Series, UNC School of Medicine
1990-1993	Mentor and Supervisor, Neuropsychology Clinical Post-doctoral Fellows and Pre-
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1990-1993	Mentor for Psychiatry Research Fellows, Research Fellowship Training Program, UNC
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1990-1993	Member, Training Faculty Institutional National Research Service Award Fellowship
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1990-1993	Co-director, Neuropsychiatry Seminar Series, UNC School of Medicine
1990-1993	Regular lecturer, Consult/Liaison Seminar Series, UNC Psychiatry Residency Training
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1990-1993	Co-director, "Brain-Behavior Relationships", 3 rd year medical school course; UNC
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1990-1993	Regular Lecturer, 1st year Neurobiology Course, UNC School of Medicine
1990-1993	Regular Lecturer, "Adult Language Disorders" Course, Division of Speech and Hearing
	Sciences; UNC School of Medicine
1990-1993	Regular Lecturer, Graduate Neuropsychology Course, UNC
1990-1993	Regular Lecturer, Undergraduate Neuropsychology Seminar, UNC
1993	Non-faculty member of Ph.D. Dissertation Committees; Suffolk University, North
	Carolina State University, University of Alabama, University of New South Wales,
	Australia
1993-2003	Member, Neuropsychology Training Faculty; mentored clinical and research
1000 0000	neuropsychology fellows and interns; Brown University
1993-2003	Supervised research placements for neuropsychology pre-doctoral interns; Brown
1002 2002	University
1993-2003	Regular lecturer for Neuropsychology Seminar Series, Brown Medical School
1993-2003	Regular lecturer for Neuropsychology Rounds, Brown Medical School
1993-2003	Training Faculty, Neuropsychiatry/Behavioral Neurology Fellowship, Depts. Of
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1993-2003	
1993-2003	Regular lectures for Post-doctoral Fellow Lecture Series; Clinical Psychology Training
1993-2003	Consortium, Brown Medical School Lecturer for Psychiatry Residency Training Program for PGY 1, 2, 3 and 4 Lecture
1993-2003	Series, Brown Medical School
1993-2003	Lecturer for First Year Medical Students Medical Interviewing Seminar, Brown Medical
1773-2003	School
1993-2003	Mentor for Undergraduate Independent Study Courses, Departments of Neuroscience,
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1993-2004	Supervised Practicum Training Site for Clinical Psychology Graduate Students,
1995 2001	Undergraduate Psychology Internship Placement; URI
1994-Present	Annual lecturer for Basic Neurosciences Course, Behavioral Neurosciences Program,
	BUSM
1999-2007	Clinical Practicum Supervisor; Suffolk University Clinical Psychology Program
2001–2002	Coordinator, Internship Training Program Neuropsychology Track, Brown University
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2001-2002	Training Committee Member; Brown University Clinical Psychology Training Consortium
2003	Core Faculty Member, Brown University T32 Dementia Research Training Program
2004-Present	Annual lecturer for Human Neuropsychology Seminar, Behavioral Neurosciences
2004-Flesent	Program, BUSM
2004-Present	Lecturer for Neurology Residency Training Program Lecture Series
2005-2007	Advisor (for 40 graduate students), BUSM Graduate Medical Sciences Masters Program
2005-Present	Director, Post-Doctoral Neuropsychology Training Program, Alzheimer's Disease
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2005-Present	Director and Lecturer for Neuropsychology and Dementia Seminar Series, Geriatric
	Medicine, Dentistry & Psychiatry Fellowship Program
2005-Present	Consulting Neuropsychologist and Research Mentor, APA Accredited Internship and
	Fellowship Clinical Neuropsychology Training Program; Bedford (MA) Veterans Affairs
	Medical Center
2006-2008	Course Co-Director, Neuropsychological Assessment, Behavioral Neurosciences
2000 2000	Program, BUSM
2007-2008	Lecturer for Biology of Disease (Neurology) Course, BUSM Preclinical Medical School
2007 2000	Course
2010-Present	CME Annual Course Co-Director, Brain Trauma and the Athlete, BUSM
2011-Present	Core Faculty Member, Alzheimer's Disease Translational Research Training Program
2011-11CSCIII	
2012 P	(National Institute on Aging T32), BUSM
2012-Present	CME Course Co-Director, Chronic Traumatic Encephalopathy, co-sponsored by BUSM
	and the Cleveland Clinic Lou Ruvo Center for Brain Health; Las Vegas, September 30-
	October 1, 2012

MAJOR MENTORING ACTIVITIES:

<u>Undergraduate Honors Theses Supervised</u>

- 1991 Wendy Cox, "Effects of Physostigmine on Mood and Sustained Attention," Psychology Department, University of North Carolina
- Boykin Robinson, "Self-Report of Emotional and Cognitive Complaints in Individuals with Graves' Disease: A Survey Study," Psychology Department, University of North Carolina
- 1996 Mara Lowenstein, "Neuropsychological Functioning in Alzheimer's Disease and Vascular Dementia: A Qualitative Assessment of the Rey-Osterrieth Complex Figure," Psychology Department, Brown University
- 1997 Yamini Subramanian, "The Thyroid Axis and Seizure Threshold: Examining a Mechanism of Thyroid Hormone Augmentation of ECT," Neuroscience Department, Brown University
- 2002 Anna Podolanczuk, "Thyroid Hormone Levels in Post-Mortem Alzheimer's and Control Brains," Neuroscience Department, Brown University

Master's Theses Supervised

- 1998 Jennifer Latham, "The Visual Analog Mood Scales for Adolescents : A Preliminary Examination of Reliability and Validity," Psychology Department, University of Rhode Island
- 2000 Jessica Somerville, "A Comparison of Administration Procedures for the Rey-Osterrieth Complex Figure: Flow-Charts Vs. Pen-Switching," Psychology Department, University of Rhode Island
- 2000 Susan L. Legendre, "The Influence of Cognitive Reserve on Memory After Electroconvulsive Therapy," Psychology Department, University of Rhode Island
- 2005 Veronica Santini, "Thyroid-Neurobehavioral Relationships in the Elderly," Division of Graduate Medical Sciences, Boston University School of Medicine

- 2006 Daniel Daneshvar, "Association between Smoking, APOE, and Risk for Mild Cognitive Impairment and Alzheimer's Disease," Division of Graduate Medical Sciences, Boston University School of Medicine
- 2006 Laura Ridgely, "The Public Health Risk of Unsafe Elderly Drivers and Drivers with Dementia: Current Problems and Steps to be Taken," Division of Graduate Medical Sciences, Boston University School of Medicine
- 2007 David Essaff, "Executive Dysfunction in Early Alzheimer's Disease (AD) and Mild Cognitive Impairment: A Potential Cognitive Marker for Preclinical AD," Division of Graduate Medical Sciences, Boston University School of Medicine
- 2007 Meghan Lembeck, "Racial Disparities and Mild Cognitive Impairment Diagnosis: The Effects of Literacy Correction on Neuropsychological Test Scores," Division of Graduate Medical Sciences, Boston University School of Medicine
- 2008 Jessica A. Riggs, "Current Approaches to Alzheimer's Disease Treatment: A Focus on Passive Immunotherapy," Division of Graduate Medical Sciences, Boston University School of Medicine
- 2009 Vlada Doktor, "Clinical utility of Self and Informant's Complaint in Mild Cognitive Impairment and the Rate of Progression to Alzheimer's Disease," Division of Graduate Medical Sciences, Boston University School of Medicine
- 2011 John Picano, "Defining Concussions: A Literary and Empirical Analysis of Sports-Related Concussion."
- 2013 Alexandra Bourlas, "The Effects of Level and Duration of Play on Cognition, Mood and Behavior Among Former Football Players."

Doctoral Dissertations Supervised

- 1991 Susan L. Silva, "The Effects of Physostigmine on Cognition, Mood, and Behavior," Department of Psychology, North Carolina State University
- 1993 Mark L. Prohaska, "Thyroid, Lithium, and Cognition: The Use of Thyroid Hormone Augmentation in the Reduction of Cognitive Side Effects Associated with Lithium Maintenance," Psychology Department, University of Alabama
- 1999 Debbie J. Javorsky, "A Validation Study of the Boston Qualitative Scoring System (BQSS) for the Rey-Osterrieth Complex Figure," Psychology Department, University of Rhode Island
- 2003 Susan L. Legendre, "The Influence of Cognitive Reserve on Neuropsychological Functioning After Coronary-Artery Bypass Grafting (CABG)," Psychology Department, University of Rhode Island
- Jessica Somerville Ruffolo, "Visuoconstructional Impairment: What Are We Assessing and How Are We Assessing It?," Psychology Department, University of Rhode Island
- 2014 Stacy Anderson, "Episodic Memory and Executive Function in Familial Longevity" (Second Reader), Behavioral Neurosciences Program, Boston University School of Medicine.

Current PhD and MD/PhD Students

Julie Stamm (Mentor for NIH F31 Grant 1F31NS081957; 2013-Present; PhD candidate, Dept of Anatomy and Neurobiology)

Philip Montenigro (MD/PhD candidate, Dept. of Anatomy and Neurobiology)

Daniel Corps (visiting PhD student from Melborne, Australia)

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Post-Doctoral Fellows Trained		
1991-1993	Susan Silva, Ph.D., now Research Associate Professor at Duke University	
1992-1993	Mareah Steketee, Ph.D., now Adjunct Associate Professor at UNC-Chapel Hill	
1993-1995	Mark Prohaska, Ph.D., now Director, Neuropsychology Clinic, Alabama	
1994-1996	James Arruda, Ph.D., now Associate Professor at University of West Florida	
1994-1996	Garrie Thompson, Ph.D., now Clinical Neuropsychologist, Florida	
1996-1998	Geoffrey Tremont, Ph.D., now Associate Professor at Brown University	
1998-2000	Holly Westervelt, Ph.D., now Clinical Assistant Professor at Brown University	
1998-2000	Debbie Javorsky, Ph.D., now Clinical Neuropsychologist, New Hampshire	
2000-2001	Michael Ropacki, Ph.D., now Medical Director, Global Medical Affairs, Janssen	
	Alzheimer Immunotherapy	
2000-2002	Caitlin Macaulay, Ph.D., now Clinical Neuropsychologist at Lahey Clinic, Massachusetts	
2001-2004	Jennifer Duncan Davis, Ph.D., now Assistant Professor at Brown University	
2002-2003	Richard Temple, Ph.D., now Vice President of Clinical Operations at Core Health Care	
2003-2004	Laura Brown, Ph.D., now Clinical Neuropsychologist, Rhode Island	
2003-2004	Mary Beth Spitznagel, Ph.D., now Assistant Professor at Kent State University	
2004-2005	Angela Jefferson, Ph.D., now Associate Professor at Vanderbilt University	
2005-2007	Lee Ashendorf, Ph.D., now Clinical Neuropsychologist at Bedford VAMC	
2007-2009	Brandon Gavett, Ph.D., now Assistant Professor at Univ. of Colorado, Colorado Springs	
2010-2011	Katherine Gifford, Ph.D., now Fellow at Vanderbilt University	
2012-2013	Daniel Seichepine, Ph.D.	
2012-2014	Elizabeth Vassey, Ph.D.	
2013-Present	Todd Solomon, Ph.D.	

MAJOR ADMINISTRATIVE RESPONSIBILITIES:

1991-1993	Director, Neurobehavioral Assessment Core, NIMH-funded Mental Health Clinical
	Research Center, UNC School of Medicine
1992-1993	Acting Director, Data Management/Biostatistics Core, NIMH-funded Mental Health
	Clinical Research Center, UNC School of Medicine
1992-1993	Associate Center Director, NIMH-funded Mental Health Clinical Research Center, UNC
	School of Medicine
1995-1996	Vice Chair, Committee for the Protection of the Rights of Human
	Subjects (IRB), Rhode Island Hospital
2001-2002	Coordinator of Neuropsychology Track, Internship Training Program, Brown Clinical
	Psychology Training Consortium, Brown Medical School
2004-Present	Director of Neuropsychology, Alzheimer's Disease Clinical and Research Program,
	Boston University School of Medicine (BUSM)
2004-2008	Associate Director, Alzheimer's Disease Center (NIA-Funded) Clinical Core, BUSM
2004-2006	Associate Director, Alzheimer's Disease Clinical and Research Program, BUSM
2006-2010	Co-Director, Alzheimer's Disease Clinical and Research Program, BUMC
2008-2012	Co-Director, Center for the Study of Traumatic Encephalopathy, BUSM
2009-2010	Acting Director, Alzheimer's Disease Clinical and Research Program, BUMC
2009	Acting Director, Alzheimer's Disease Center (NIA-Funded) Clinical Core, BUSM
2010-Present	Director, Alzheimer's Disease Center (NIA-Funded) Clinical Core, BUSM
2011-2012	Director, Alzheimer's Disease Clinical and Research Program, BUMC
2011-2012	Co-Chair, Global Advisory Committee, INternational Registry Of Alzheimer's Disease
	patientS (INROADS), Janssen Alzheimer Immunotherapy
2011-Present	Site Director (BU) and Steering Committee Member, Alzheimer's Disease Cooperative
	Study (NIA-Funded)
2014-Present	Director of Clinical Research, CTE Center, BUSM

OTHER PROFESSIONAL ACTIVITIES:

PROFESSIONAL SOCIETIES: MEMBERSHIPS, OFFICES, AND COMMITTEE ASSIGNMENTS

International Neuropsychological Society (Member, 1987-Present)

Member, Scientific Program Committee, 1997-1999

Meeting Development Coordinator, 1999-2001

American Psychological Association Division 40, Clinical Neuropsychology (Member, 1988-Present) Member, Scientific Advisory Committee, 1995-1997

American Psychological Association Division 12, Clinical Psychology (Member, 1988-Present)

National Academy of Neuropsychology (Member, 1990-Present)

Fellow, Appointed 2001

American Neuropsychiatric Association (Member, 1995-Present)

Fellow, Appointed 2001

Member, Scientific Program Committee, 1995-1999

Co-Director, Annual Meetings, 1997-1999

Member, Awards Committee, 2006-Present

Massachusetts Neuropsychological Society (Member, 2007-Present)

International Society to Advance Alzheimer Research and Treatment (Member, 2008-Present)

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EDITORIAL BOARDS:

1998-Present Associate Editor, Journal of Neuropsychiatry and Clinical Neurosciences

2001-2003 Consulting Editor, Assessment

2008-Present Editorial Board Member, Archives of Clinical Neuropsychology

2010-Present Review Editor, *Frontiers in Neurotrauma* 2011-Present Review Editor, *Frontiers in Sports Neurology*

2012-Present Series Editor, Traumatic Brain Injury Series, *Alzheimer's Research and Therapy*

JOURNAL REVIEWER

Alzheimer's Disease and Associated Disorders

Archives of Neurology

Brain and Cognition

Cognitive and Behavioral Neurology

Injury Epidemiology

International Journal of Geriatric Psychiatry

International Review of Psychiatry

Journal of Clinical and Experimental Neuropsychology

Journal of the International Neuropsychological Society

Journal of the Neurological Sciences

Journal of Nutrition, Health and Aging

Neurology

Neurology: Clinical Practice

Neurology Psychiatry & Brain Research

Neuropsychology

Neuroscience & Biobehavioral Reviews

PLOS ONE

The Clinical Neuropsychologist

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MAJOR COMMITTEE ASSIGNMENTS:

Federal Governmen	nt end of the control		
1998 - 1999 Independent Neuropsychological Review Committee V.A. Cooperative Study #0			
	"Evaluation of a Computer-Assisted Neuropsychological Screening Battery", Department		
	of Veterans Affairs		
2012 – Present	Member, Advisory Board, DoD ADNI (Effects of traumatic brain injury and post		

traumatic stress disorder on Alzheimer's disease in Veterans using ADNI; PI: MW

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1993-Present	Member, Medical Advisory Board, National Graves' Disease Foundation
2007-Present	Member, Medical Advisory Board, Sports Legacy Institute
2007-Present	Member, Medical & Scientific Advisory Committee, Massachusetts/New Hampshire
	Chapter, Alzheimer's Association
2010-Present	Member, Mackey-White Traumatic Brain Injury Committee, National Football League
	Players Association: Co-Chair of Subcommittee on Former Player Research

Study Sections

National Institutes of Health			
1993	Ad hoc Reviewer, Mental Health AIDS and Immunology Review Committee:		
	Psychobiological, Biological, and Neuroscience Subcommittee		
1995	Ad hoc Reviewer, Mental Health Small Business Research Review		
1995-1996	Reviewers Reserve (NRR; Study Sections) Member		
1996-1998	Mental Health Small Business Research Review Committee Member		
1999	Ad hoc Reviewer, Small Business Research Review Committee		
2000	Ad hoc Reviewer, Special Emphasis Panel – ZMH1-CRB-B01		
2013	Ad hoc Reviewer, Special Emphasis Panel - ZRG1 BBBP-D02		

Other National Review Committees

1998-Present	Initial Review Board of the Medical and Scientific Advisory Council, Alzheimer's
	Association

2013 Reviewer, US Army Medical Research and Materiel Command (USAMRMC)

International

1991-1992

2013	External Advisor,	Wellcome 7	Trust Strategic <i>A</i>	Award Committee	(SAC)

CONSULTANT ACTIVITIES:

Cato Research, Ltd. (Clinical Trials Design and Implementation) Durham, NC

1995-2003	"HIV: Neuropsychiatric and Psychoimmune Relationships" (Dwight Evans, PI; R01
	Grant), Department of Psychiatry, University of Pennsylvania
2004-2006	"A Telephone Intervention for Dementia Caregivers" (Geoffrey Tremont, PI; R21 Grant),
	Rhode Island Hospital/Brown Medical School
2004-2006	"A Longitudinal Study of Hazardous Drivers with Dementia" (Brian Ott, PI; R01 Grant),
	Memorial Hospital of Rhode Island/Brown Medical School
2007-2009	Outcome Science (for Forest Laboratories), Cambridge, MA
2000	

Elan Pharmaceuticals, San Francisco, CA

Neuronix, Yokneam, Israel

2012 Lilly (Expert Advisor), Indianapolis, IN

2011-2012 Janssen Alzheimer Immunotherapy, San Francisco, CA

2013-Present Athena Diagnostics (Quest), Worcester, MA

CURRENT OTHER SUPPORT:

2014-2015	2R56NS078337-04, PI: Stern , Chronic Traumatic Encephalopathy: Clinical Presentation and Biomarkers (competing continuation), Total Costs: \$785,813.
2014-2018	ADCS-Toyama Chemical Partnership; Site PI: Stern , A Phase 2 multi-center, randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T-817MA in patients with mild to moderate Alzheimer's Disease (US202), Total Costs: \$473,346.
2014-2015	Avid Radiopharmaceuticals; PI: Stern , 18F-AV-1451 and Florbetapir F 18 PET Imaging in Subjects with Repetitive Brain Trauma at High Risk for Chronic Traumatic Encephalopathy, Total Costs: \$243,263.
2014-2015	R56NS089607, mPI: Au/McClean/Grafman (Stern Co-Investigator), Precursors and Prognosis of Traumatic Brain Injury in Young to Middle Aged Adults, Total Costs: \$634,227
2014-2016	Avid Radiopharmaceuticals; Site PI: Stern , 18F-AV-1451-A05: An open label, multicenter study, evaluating the safety and imaging characteristics of 18F-AV-1451 in cognitively healthy volunteers, subjects with Mild Cognitive Impairment, and subjects with Alzheimer's disease, Total Costs: \$395,222.
2014-2019	Alzheimer's Disease Cooperative Study (ADCS), Site PI: Stern , Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study), Total Costs: \$464,479.
2014-2019	Eli Lilly, Site PI: Stern , Effect of Passive Immunization on the Progression of Mild Alzheimer's Disease: Solanezumab (LY2062430) Versus Placebo, Total Costs: \$395,270
2014-2016	Amarantus Holdings, Inc., PI: Stern , Amarantus LymPro Cell Cycle Dysfunction Blood Biomarker for AD and CTE, Total Costs: 54,600
2013-2016	DoD W81XWH-13-2-0064; Traumatic Brain Injury Research Award; Co-PI: Stern (Co-PI: M. Shenton), Tau Imaging of Chronic Traumatic Encephalopathy, Total Costs: \$992,727
2013-2015	Eisai, Inc., Site PI: Stern , A Placebo-controlled, double-blind, parallel-group, Baysian Adaptive Randomization Design and Dose Regimen-finding study to evaluate safety, tolerability and efficacy of BAN2401 in subjects with early Alzheimer's disease, Total Costs: \$391,342.
2013-2017	U01-NS086659; PI: McKee (Stern, Co-Investigator), CTE and Posttraumatic Neurodegeneration: Neuropathology and Ex Vivo Imaging, Total Costs: \$6,000,000
2011-2015	R01NS078337-01A1, PI: Stern , Chronic Traumatic Encephalopathy: Clinical Presentation and Biomarkers, Total Costs: \$ 2,035,330.
2011-2016	P30-AG13846, PI: N. Kowall; Clinical Core Director: Stern ; Boston University Alzheimer's Disease Core Center; Total Costs: \$5,986,877.
2010-2015	D01 HP08796, PI: S. Chao; Neuropsychology Director: R.A. Stern ; Geriatric Medicine, Dentistry and Psychiatry Fellowship at Boston University; Total Direct Costs: \$1,044,630
2009-2015	R01CA129769, PI: Stern (mPI: Mandelblatt, Ahles), Older Breast Cancer Patients: Risk for Cognitive Decline, Total Costs: \$ 3,186,605

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PAST OTHER SUPPORT

2008-2014	R01MH080295, PI: Stern (MPI: R. Joffe), Subclinical Hypothyroidism: Mood, Cognition and the Effect of L-Thyroxine Treatment, Total Costs: \$ 2,229,240
2009-2013	Medivation, Inc. Protocol No. DIM18EXT, Site PI: R.A. Stern, Concert Plus: An Open-Label Extension of the Concert Protocol (DIM18) Evaluating Dimebon (Latrepirdine) in Patients with Alzheimer's Disease, Total Direct Costs: \$30,768
2009-2013	Wyeth/Pfizer Pharmacuticals, Site PI: R.A. Stern, A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) in Patients with Mild to Moderate Alzheimer's Disease who are Apolipoprotein E 4 Carriers (Protocol 3133K1-3001-US), Total Direct Costs: \$265,380
2008-2012	Elan Pharmacuticals (now Janssen Alzheimer's Immunotherapy), Site PI: R.A. Stern, A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) in Patients with Mild to Moderate Alzheimer's Disease who are Apolipoprotein E 4 Non-Carriers (Protocol ELN115727-301) and Carriers (Protocol ELN115727-302), Total Direct Costs: \$500,000
2007-2012	U01 AG10483, ADCS Contract (CFDA #93.866), Site PI: R.A. Stern, Multi-Center Trial to Evaluate Home-Based Assessment Methods for Alzheimer 's Disease Prevention Research in People Over 75 Years Old, Total Direct Costs: \$117,750
2009-2011	5U01AG015477-07 ARRA. PI: J. Breitner; Site Director: R.A. Stern, Prevention of Alzheimer's Disease and Cognitive Decline, Total Direct Costs (Boston Site): \$145,432
2009-2011	National Operating Committee on Standards for Athletic Equipment Investigator Initiated Grant, PI: A.C. McKee & R.A. Stern, Neuropathological and Clinical Consequences of Repetitive Concussion in Athletes; Total Direct Costs: \$249,992
2008-2011	IIRG-08-89720 (Alzheimer's Association), PI: R.A. Stern, Assessment of Driving Safety in Aging, MCI and Dementia, Total Direct Costs: \$240,000
2008-2011	Alzheimer's Association Subcontract, PI: G. Feke; Site PI: R.A. Stern, Objective Biomarkers for Alzheimer's Disease in the Retina, Total Costs: \$81,000 Subcontract
2009-2010	P30-AG13846 Supplement to P30 Center Grant, PI: R.A. Stern & A.C. McKee (N. Kowell, P30 PI); Development of Pathology Diagnostic Criteria for Chronic Traumatic Encephalopathy, Total Direct Costs: \$83,287
2008-2009	P30-AG13846 Supplement to P30 Center Grant, PI: R.A. Stern & A.C. McKee (N. Kowell, P30 PI); Neuropathologic Examination of Traumatic Encephalopathy in Athletes with Histories of Repetitive Concussion, Total Direct Costs: \$100,000
2004-2009	U01 AG023755, PI: T. Perls, Exceptional Survival and Longevity in New England, Total Direct Costs: \$2,073,781
2006-2009	R01 HG/AG02213, PI: R.C. Green, Risk Evaluation and Education for Alzheimer's Disease (REVEAL III), Total Direct Costs: \$1,992,415
2000-2007	U01 AG15477, PI: J. Breitner, The ADAPT Study: Alzheimer's Disease Anti-inflammatory Prevention Trial, Total Direct Costs to Boston Site: \$561,246
2004-2006	Massachusetts Institute of Technology AgeLab and The Hartford, PI: R.A. Stern; Driving and Dementia Total Direct Costs: \$162,082
2004-2005	Boston University Alzheimer's Disease Core Center Pilot Project Grant, PI: R.A. Stern Triiodothyronine Treatment of Alzheimer's Dementia, Total Direct Costs: \$29,989

CV: Robert A. Stern, F	Ph.D Page 12
2001-2004	R21MH062561, PI: G. Tremont, A Telephone Intervention for Dementia Caregivers, Total Direct Costs: \$375,000
2001-2005	5R01AG016335, PI: B. Ott, A Longitudinal Study of Hazardous Drivers with Dementia, \$103,008, Subcontract
1998-2004	5R01NS037840, PI: Ivan Miller. Title: Efficacy of a Family Telephone Intervention for Stroke, Total Direct Costs: \$1,516,615
2000-2003	Eisai, Inc. and Pfizer, Inc Investigator Initiated Grant, PI: R.A. Stern; Title: Clinical Trial of Donepezil Hydrochloride (Aricept) in Diminishing the Cognitive Impairment Associated with Electroconvulsive Therapy; Total Direct Costs: \$108,854
1999-2003	Alzheimer's Association Individual Research Grant; PI: R.A. Stern; Title: A Double-Blind Study of Donepezil with and without Thyroid Hormone in the Treatment of Alzheimer's Dementia Total Direct Costs; \$163,626
2000-2002	R44 MH58501, PI: T. White. Project PI: R.A. Stern; Title: A Modular Neuropsychological Test Battery (Subcontract with Psychological Assessment Resources, Inc) Total Direct Costs: \$272,487, Subcontract (Project Total Direct: \$1,305,245)
1999-2000	Psychological Assessment Resources, Inc. Contract; PI: R.A. Stern; Title: Development of a Modular Neuropsychological Test Battery; Total Direct Costs: \$48,084
1999-2004	Thyroid Research Advisory Council (TRAC) Individual Grant; PI: Geoffrey Tremont; Title: Cerebral Perfusion and Neuropsychological Functioning in Thyrotoxic Graves' Disease Patients; Total Direct Costs: \$55,139
1997-2000	National Alliance for Research on Schizophrenia and Depression Independent Investigator Award; PI: R.A. Stern; Title: Thyroxine Treatment of the Neurocognitive Side Effects of Lithium; Total Direct Costs: \$92,592
1998	R43 MH58501-01; PI: T. White; A Modular Neuropsychological Test Battery (subcontract) Total Direct Costs: \$23,463, Subcontract
1997-1998	Research Fellowship Training Grant, Brown University Department of Psychiatry and Human Behavior; PI: Geoffrey Tremont and R.A. Stern; Psychiatric and Neuropsychologic Consequences of Graves' Disease; Total Direct Costs: \$15,888
1996-1997	Contract, Milkhaus Laboratory; PI: R.A. Stern; An Open-Label Treatment of 2CVV in the Amelioration of Neuropsychological and Psychiatric Symptoms Associated with Chronic Fatigue Syndrome (CFS); Total Direct Costs: \$10,000
1995-1996	Contract, Milkhaus Laboratory; PI: R. A. Stern; 2CVV in the Amelioration of Neuropsychological and Psychiatric Symptoms in Outpatients with Chronic Fatigue Syndrome: A Phase 1/2, Double-Blind, Placebo-Controlled Study; Total Direct Costs: \$9575
1994-1995	Research Fellowship Training Grant (PI: James Arruda, Ph.D., Fellow); Title: Neurobehavioral Functioning in Women Infected with HIV-1; Total Direct Costs: \$17,500
1992-1997	5R01MH048578-05; PI: R.A. Stern; Combined Thyroid Hormone and Electroconvulsive Therapy; Total Direct Costs: \$471,021
1992-1994	5R01MH043231-02; PI: J.J.Haggerty; Co-PI: R.A. Stern; Neuropsychiatric Aspects of Marginal Hypothyroidism; Total Direct Costs: \$174,413
1992-1997	5P50MH033127; PI: A.J. Prange, Jr.; Neurobehavioral Assessment Core Director: R.A. Stern; Psychoendocrinology: Children and Adults, Total Direct Costs: \$4,641,038 total project; \$256,624 subproject [core] *role in project ended 7/93 due to leaving UNC

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CV: Robert A. Stern, I	Ph.D Page 13	
1992-1993	UNC University Research Council Pilot Project Award Grant; PI: R. A. Stern; Influence of L-triiodothyronine (T3) on Memory following Repeated Electroconvulsive Shock (ECS) in Rats; Total Direct Costs: \$3000	
1992-1993	The Psychological Corporation Contract; PI: R.A. Stern; Validation of the Microcog Computerized Neuropsychological Screening Test in HIV-Infected Gay Men; Total Direct Costs: \$3600	
1991-1992	UNC Medical Faculty Research Pilot Project Award Grant; PI: R.A. Stern; Physostigmine as a Psychodiagnostic Tool: The Effects of Physostigmine on Cognition, Mood, and Behavior in Normal Volunteers; Total Direct Costs: \$3000	
1990-1992	The Foundation of Hope for Research and Treatment of Mental Illness Pilot Project Award; PI: R.A. Stern; Neuropsychological Correlates of Pregnancy and the Early Puerperium; Total Direct Costs: \$16,000	
1990-1992	The North Carolina Foundation for Mental Health Research, Inc. Pilot Project Award; PI: R.A. Stern; Physostigmine as a Psychodiagnostic Tool: The Effects of Physostigmine on Cognition, Mood and Behavior; Total Direct Costs: \$1200	
1989-1991	The Foundation of Hope for Research and Treatment of Mental Illness Pilot Project Award; PI: R.A. Stern; Neuropsychological Correlates of Alterations in Thyroid State; Total Direct Costs: \$26,317	
1989-1994	R01MH044618; PI: D. Evans; HIV: Neuropsychiatric and Psychoimmune Relationships; Total Direct Costs: \$1,293,290 (subcontract)	
	CONGRESSIONAL TESTIMONY	
June 25, 2014	Special Committee on Aging, United States Senate Hearing on "State of Play: Brain Injuries and Diseases of Aging"	
	T	
	INVITED LECTURES AND PRESENTATIONS (Does not include frequent invited community lay lectures, including lectures for the MA/NH Chapter of the Alzheimer's Association)	
May 16, 1989	Mood Disorders and Cerebrovascular Disease. Department of Psychiatry, Rhode Island Hospital, Brown University School of Medicine, Providence, RI,.	
Dec. 8, 1989	Mood Disorders following Stroke. Continuing Education Course, Greensboro (NC) Area Health Education Center,	
January 4, 1990	Assessment and Diagnosis of Post-Stroke Mood Disorders. Continuing Education Course, Westboro (MA) State Hospital	

September 22, 1990 *Theories and Models of Human Cognition: Learning and Memory*. Advanced Workshops in Traumatic Brain Injury Rehabilitation, Peace Rehabilitation Center, Greenville, SC.

Workshop, Mountain Area Health Education Center, Asheville, NC

Center, Bowman-Gray Medical Center, Winston-Salem, NC

Research in Psychiatry. Chapel Hill, NC.

How to Design a Clinical Trial. Third annual meeting of the Southern Association for

Assessment and Diagnosis of Post-Stroke Mood Disorders. Whittiker Rehabilitation

Neurobehavioral Syndromes: Assessment and Diagnosis. Continuing Education

March 3, 1990

May 25, 1990

Aug 17, 31 1990

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Center, Boston, MA

November 15, 1994 Brain-Behavior Relationships: Appropriate Use and Benefits of Neuropsychological Evaluation. Grand Rounds. Department of Medicine, Rhode Island Hospital, Providence, RI

November 17, 1994 Neuropsychiatric Aspects of HIV and AIDS. General Internal Medicine Research Seminar. Rhode Island Hospital, Providence, RI.

March 5, 1996 Thyroid Disorders and Psychiatry. Grand Rounds, St. Luke's Hospital, New Bedford, MA

March 26, 1996 Neurobehavioral Aspects of Thyroid Disorders. Lecture Series, Department of Endocrinology, University of Virginia School of Medicine, Charlottesville, VA

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April 10, 1996	Neuropsychiatric Aspects of Thyroid Disorders. Psychiatry Lecture Series, Rhode Island Hospital, Providence, RI
April 19, 1996	Neurobehavioral Aspects of Graves' Disease. Keynote Address, Third Annual Meeting of the New England Thyroid Club, Westborough, MA
May 7, 1996	Neuropsychological Evaluation of Executive Functioning. "Neuropsychiatry for Clinicians" section of the <i>Psychiatry Update</i> session of the 149th Annual Meeting of the American Psychiatric Association, New York
June 19, 1997	Assessment of Mood State and Depression in Neurodegenerative Disease. Geriatric Case Conference and Journal Club. Butler Hospital
November 2, 1997	<i>The Thyroid Axis in Mood Disorders: Thoughts About Therapy</i> (Discussant). The 14th Annual George C. Ham Symposium (A Festschrift Celebrating the Career of Arthur J. Prange, Jr.). Chapel Hill, NC
December 19, 1997	Neuropsychiatric Manifestations of HIV Infection. Psychiatry Grand Rounds. Department of Veterans Affairs Medical Center. Providence, RI
May 5, 1998	Quantifying the Qualitative Features of Rey-Osterrieth Complex Figure Performance: The Boston Qualitative Scoring System (BQSS). Continuing Education Lecture. Massachusetts Neuropsychological Society, Boston, MA
November 8, 1998	Assessment of Mood State and Depression in Aphasia. Assessment, Treatment, and Emotional Issues Symposium. 19th Annual Neurorehabilitation Conference on Traumatic Brain Injury and Stroke. (Sponsored by the Healthsouth Braintree Rehabilitation Hospital.) Cambridge, MA
April 27, 1999	Assessment of Mood and Depression in Neurologic Disease. Spring Lecture Series. Department of Communicative Disorders, University of Rhode Island, Kingston, RI
June 16, 1999	The Use of Thyroid Hormone to Diminish the Cognitive Side Effects of Psychiatric Treatment. Psychiatry Grand Rounds, McMaster University Medical Center, Hamilton, Ontario, Canada
Nov. 13, 1999	Cognitive Rehabilitation: A Neuropsychological Perspective. "Frontiers of Hope;" Annual National Meeting for Patients, Families, and Health Care Professionals; Brain Tumor Society, Providence, RI
March 1, 2000	Neurobehavioral Functioning in Thyroid Disease. Neurology Grand Rounds, Brown University School of Medicine, Rhode Island Hospital, Providence, RI
June 14, 2000	Surviving a Brain Tumor: Understanding Changes in Thinking and Memory. Featured speaker for an international educational teleconference for brain tumor survivors and family members, co-sponsored by the Brain Tumor Society, the American Brain Tumor Association, the National Brain Tumor Foundation, and Cancer Care, Inc.
December 14, 2000	The Use of Thyroid Hormone to Diminish the Cognitive Side Effects of ECT and Lithium. Geriatric Psychiatry Case Conference and Journal Club (CME activity), Butler Hospital, Providence, RI
April 29, 2002	The Thyroid-Brain Connection: Neuropsychological and Behavioral Aspects of Thyroid Disorders. Keynote Speaker, Psi Chi Induction Ceremony, Providence College, Providence, RI
September 21, 2002	The Invisible Disability: Living with the Cognitive and Behavioral Changes from a Brain Tumor. "Living Beyond a Brain Tumor 2002: A brain tumor symposium for patients, families, and healthcare professionals. Brain Tumor Society, Quincy, MA

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December 5, 2002	Neuropsychology of Thyroid Disease. Behavioral Neuroscience Seminar Series. Brigham and Women's Hospital, Harvard Medical School, Boston, MA
June 16, 2003	The Role of Thyroid Functioning in the Aging Brain and Dementia. Seminar Series, Alzheimer's Disease Center, Boston University School of Medicine, Boston, MA
December 12, 2003	The Neuropsychological Assessment Battery (NAB). Continuing Education Workshop, Colorado Neuropsychological Society, Denver, CO
January 23, 2004	<i>The Neuropsychological Assessment Battery (NAB)</i> . Continuing Education Workshop, Georgia Psychological Association, Emerald Pointe, GA,.
January 24, 2004	The Neuropsychological Assessment Battery (NAB): Development and Psychometric Properties. Continuing Education Workshop, 1 st Professional Neuropsychology Weekend Conference, Coalition of Clinical Practitioners in Neuropsychology, Las Vegas, NV
January 24, 2004	The Neuropsychological Assessment Battery (NAB): Administration, Scoring, and Interpretation. Continuing Education Workshop, 1 st Professional Neuropsychology Weekend Conference, Coalition of Clinical Practitioners in Neuropsychology, Las Vegas, NV
April 1, 2004	The Utility of the Neuropsychological Assessment Battery (NAB) in the Evaluation of Adult Neurodevelopment Disabilities. Continuing Education Workshop, Annual Conference of Contemporary Applications of Psychological Testing, Harvard Medical School, Boston, MA
October 8, 2004	The Neuropsychological Assessment Battery (NAB). Workshop presented at the annual meeting of the International Test Commission, Williamsburg, VA
December 8, 2004	The Role of Thyroid Functioning in the Aging Brain and Dementia. Psychiatry Grand Rounds, Edith Norse Veterans Administration Medical Center, Bedford, MA
February 5, 2005	<i>Neurobehavioral Functioning in Thyroid Disorders</i> . Continuing Education Seminar presented at the 32 nd Annual Conference of the International Neuropsychological Society, Las Vegas, NV
March 15, 2005	Thyroid-Brain Relationships in Aging and Dementia. Neurology Grand Rounds, Boston University School of Medicine, Boston, MA
March 22, 2005	Cognitive & Memory Changes in Aging & Dementia. Mini-Med School, Boston University School of Medicine, Boston, MA
May 12, 2005	Alzheimer's Disease Research in 2005: Where are we and Where are we Going? Keynote Address, 5 th Annual Boston Alzheimer's Partnership Legislative Breakfast. Dorchester, MA
June 7, 2005	Alzheimer's Disease Research in 2005. Keynote Address, "Alzheimer's Disease: Finding New Pathways," Berkshire Area Health Education Center Conference, Hancock, MA.
May 3, 2006	Research Update. Alzheimer's Association annual "Map Through the Maze," Marlboro, MA
June 4, 2006	<i>Advances in Alzheimer's Disease: Diagnosis and Care of Women.</i> 14 th Annual Congress on Women's Health, Hilton Head, SC
January 16, 2007	New Discoveries and Directions in Alzheimer's Disease Research and Care. A Briefing for the Bipartisan Congressional Task Force on Alzheimer's Disease. The Rayburn House Office Building, Washington, DC,

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May 2, 2007	Research Update. Alzheimer's Association annual "Map Through the Maze," Marlboro, MA	
June 29, 2007	Driving and Dementia. Social Work Practice with Older Adults: A Continuing Education and Certificate Training Opportunity, Boston College Graduate School of Social Work, Boston, MA	
February 28, 2008	Medical Advances in Research and Treatment, Keynote Address for the Dementia/Alzheimer's Disease Training Session, Massachusetts Assisted Living Facilities Association (MassALFA), Waltham, MA.	
May 14, 2008	Driving and Dementia: Balancing Personal Independence and Public Safety. Alzheimer's Association annual "Map Through the Maze," Marlboro, MA	
June 27, 2008	Elderly Drivers: A Difficult Balance of Personal Independence & Public Safety. Women's Health and Older Adult Conference, Nurse Practitioner Associates Continuing Eduction (NPACE), Falmouth, MA	
March 6, 2009	Chronic Traumatic Encephalopathy: Progressive Tauopathy following Repetitive Concussion in Athletes, Pediatric Neurology Grand Rounds, Boston University School of Medicine	
May 13, 2009	Research Update. Alzheimer's Association annual "Map Through the Maze," Marlboro, MA	
October 2, 2009	Chronic Traumatic Encephalopathy and the Athlete. Concussion and the Athlete CME Conference, Foxboro, MA	
October 7, 2009	Alzheimer's Disease Research Update. Massachusetts Councils on Aging Annual Conference, Sturbridge, MA	
November 12, 2009	Recognizing, Diagnosing, and Treating Alzheimer's Disease. Pri-Med East CME Conference, Boston, MA	
November 13, 2009	Alzheimer's Disease Research Update 2009: Where are we Now and Where are we Going? Keynote Address at the 12 th Annual Alzheimer's Awareness Conference, Alzheimer's Services of Cape Cod and the Islands, Mashpee, MA	
March 17, 2010	<i>Chronic Traumatic Encephalopathy</i> . Briefing to the Congressional Brain Injury Task Force, Washington, DC	
June 23, 2010	Chronic Traumatic Encephalopathy and Repetitive Brain Trauma in Athletes, Institute of Medicine Committee on Nutrition, Trauma and the Brain, Washington, DC	
October 1, 2010	Long-Term Effects of Repetitive Concussive and Subconcussive Brain Trauma: Chronic Traumatic Encephalopathy (CTE). 2010 Head Trauma and the Athlete CME Conference, Waltham, MA	
October 28, 2010	The Role of Thyroid Functioning in the Aging Brain. Psychiatry Grand Rounds, Edith Norse Veterans Administration Medical Center, Bedford, MA	
November 6, 2010	Head Games: Chronic Traumatic Encephalopathy Following Repetitive Brain Trauma in Athletes. Keynote Address at the 31 st Annual Braintree Neurorehabilitation Conference, Cambridge, MA	
November 18, 2010	Alzheimer's Disease 2010: A Time for Hope, Keynote Address for the Dementia/Alzheimer's Disease Training Session, Massachusetts Assisted Living Facilities Association (MassALFA), Hopkinton, MA.	

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February 2, 2011	Chronic Traumatic Encephalopathy: Long-term Consequences of Repetitive Brain Trauma. Continuing Education Course at the 39 th Annual Meeting of the International Neuropsychological Society, Boston, MA.
March 19, 2011	Chronic Traumatic Encephalopathy, Keynote Speaker, "New Frontiers in Traumatic Brain Injury: Update 2011 Essential Information for the Clinical Neurologist," sponsored by the Massachusetts Neurologic Association and the Massachusetts Medical Society, Boston, MA.
March 25, 2011	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Impact of Repetitive Brain Trauma in Athletes, Luncheon Keynote Address, American Neuropsychiatric Association, Denver, CO
April 28, 2011	Sports Concussions: The Hidden Risks, Invited Speaker for Brain Trauma Symposium, The Neuroscience Institute at the University of Tennessee Health Science Center, Memphis, TN.
April 29, 2011	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Neurology Grand Rounds, University of Tennessee Health Sciences Center.
May 11, 2011	Driving and Dementia: A Difficult Balance of Personal Independence and Public Safety. Alzheimer's Association annual "Map Through the Maze," Marlboro, MA.
August 5, 2011	Chronic Traumatic Encephalopathy: The Synergy of Science and Journalism in Creating Culture Change. Invited Lecture at the Annual Meeting of the American Psychological Association, Washington, DC.
September 24, 2011	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Keynote Speaker for the Baptist Hospital Annual Brain Injury Symposium, Coconut Grove, FL.
October 19, 2011	Head Games: Chronic Traumatic Encephalopathy and the Long Term Effects of Repetitive Brain Trauma in Athletes. Grand Rounds Speaker, Beth Israel Deaconess Medical Center-Needham, Needham, MA
October 20, 2011	Panelist, "Alzheimer's Forum," WBUR (NPR), Boston, MA
November 5, 2011	Alzheimer's disease: Research Updates on Diagnosis, Treatment and Prevention. Keynote Speaker, Alzheimer's Association, Chicopee, MA
January 19, 2012	Chronic Traumatic Encephalopathy. Invited Lecture, Boston Society of Neurology and Psychiatry, Boston, MA
March 5, 2012	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Invited Speaker, Boston Surgical Society, Boston, MA
March 28, 2012	Moderator, Annual Alzheimer's Association (MA/NH Chapter) Research Day, Lexington, MA
April 11, 2012	Alzheimer's Disease 2012: A Reason for Hope. Keynote Speaker, Annual Research Program, Alzheimer's Association, Worcester, MA
April 17, 2012	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Grand Rounds Speaker, Good Samaritans Medical Conter Brookton MA

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Center, Brockton, MA

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April 26, 2012	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Invited Speaker, CME Series, Vista Health System, Waukegan, IL	
April 28, 2012	Alzheimer's Disease: Research Updates on Diagnosis, Treatment and Prevention. Keynote Speaker, Alzheimer's Partnership, Andover, MA	
May 16, 2012	Driving and Dementia: A Difficult Balance of Personal Independence and Public Safety. Alzheimer's Association annual "Map Through the Maze," Marlboro, MA.	
May 24, 2012	Chronic Traumatic Encephalopathy: Long-Term Effects of Repetitive Brain Trauma in Athletes and the Military. Invited Speaker, Alzheimer's Disease: Update and Research, Treatment, and Care, Annual Conference sponsored by the Shiley-Marcos Alzheimer's Disease Research Center, University of California, San Diego, San Diego, CA	
June 13, 2012	Head Games: Long-term Consequences of Repetitive Brain Trauma. Keynote Speaker, Traumatic Brain Injury Conference, Sunnybrook Hospital, Toronto, Canada	
June 15, 2012	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Keynote Speaker, "Effects of Multiple ABI—Preventing Further Injury" Conference, Brain Injury Association, London, Ontario, Canada	
August 3, 2012	Chronic Traumatic Encephalopathy. Plenary Speaker, Annual Meeting of the American Psychological Association, Orlando, FL	
October 1, 2012	Clinical Presentation of CTE: Combining Clinical and Biomarker Data for Accurate Diagnosis. Invited Speaker (and Conference Co-Chair), Inaugural Chronic Traumatic Encephalopathy (CTE) Conference, Jointly Sponsored by Boston University and the Lou Ruvo Center for Brain Health, Las Vegas, NV	
October 13, 2012	Differentiating chronic traumatic encephalopathy from Alzheimer's disease and other neurodegenerative conditions. Invited Speaker, Fred Kavli Public Symposium, Society for Neuroscience, New Orleans, LA	
October 26, 2012	Chronic Traumatic Encephalopathy: Clinical Presentation. Invited Speaker (and Conference Co-Chair), 2012 Brain Trauma and the Athlete Conference, CME Conference Sponsored by Boston University School of Medicine, Waltham, MA	
October 29, 2012	Understanding the Continuum of MCI due to AD & Dementia due to AD. Invited Speaker, Aging or Alzheimer's Disease? How to Detect and Treat Memory Loss in the Primary Care Setting, CME Conference by Boston University Alzheimer's Disease Center, Waltham, MA.	
November 10, 2012	Alzheimer's Disease 2012: Reasons for Hope. Keynote Speaker, NH Alzheimer's Association Conference: Care to Cure, Concord, NH.	
December 1, 2012.	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Invited Speaker, 59th Annual Meeting of the Massachusetts Chapter of the American College of Surgeons, Boston, MA	

- December 5, 2012 Clinical Presentation of CTE: Invited Speaker, 1st NIH Workshop on the Neuropathology of Chronic Traumatic Encephalopathy, Bethesda, MD.
- December 11, 2012 Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes. Invited Speaker, Clinical Neurosciences Grand Rounds, Boston University School of Medicine, Boston, MA
- Clinical Presentation of Chronic Traumatic Encephalopathy, Invited Speaker, 3rd March 6, 2013 Traumatic Brain Injury Conference, Arlington, VA

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March 17, 2013	Efforts toward earlier Alzheimer's Treatment, Invited Panelist, Health Journalism 2013 (American Health Care Journalists), Boston, MA	
April 17, 2013	Head Games: Chronic Traumatic Encephalopathy and the Long Term Consequences of Repetitive Brain Trauma in Athletes. Invited Webinar Speaker, Rose® Webinar Series.	
May 4, 2013	CTE and Late Life Issues, Invited Speaker, International Sports Concussion Symposium, Minneapolis, MN	
May 10, 2013	BU A Leader in Sports-Related Head Injury: Long Term Consequences, Invited Speaker, Medical Grand Rounds, Boston University School of Medicine, Boston, MA	
May 13, 2013	Clinical Presentation and Diagnosis of Chronic Traumatic Encephalopathy, Invited Speaker, World Brain Mapping Conference, Baltimore, MD	
May 31, 2013	Chronic Traumatic Encephalopathy, Invited Speaker, "Dementia: A Comprehensive Update" Continuing Medical Education Course, Harvard Medical School, Boston, MA.	
June 3, 2013	The Future of Contact Sports: Concussions May Be the Tip of the Iceberg. Invited Panelist and Speaker, The German Center for Research and Innovation and Ludwig-Maximilians-Universität München, New York, NY	
June 10, 2013	Clinical efficacy – how do we observe a potential treatment effect? Invited Speaker, Workshop: Prevention of Alzheimer's Disease – What will it take? (New York Academy of Sciences), New York, NY	
June 20, 2013	CTE: Point/Counterpoint Presentation, Invited Speaker, 11th Annual American Academy of Clinical Neuropsychology Conference, Chicago, IL	
October 24, 2013	Concussion and Action Points Symposium, The Association of Ringside Physicians 2013 Annual Medical Seminar, Las Vegas, NV	
November 12, 2013	<i>Unmet Needs in Neurodegeneration: Focus on Endpoints</i> , Keynote Speaker, 2 nd Annual Meeting of the Coalition Against Major Diseases, Bethesda, MD	
November 12, 2013	<i>Chronic Traumatic Encephalopathy: Public Health Consequences of Repetitive Brain Trauma in Sports</i> , Keynote Speaker, 2 nd Annual Research Day, Boston University School of Public Health, Boston, MA	
December 5, 2013	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes, Grand Rounds, Department of Neurology, Medical University of South Carolina, Charleston, SC	
January 17, 2014	Brain Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma, Distinguished Lecturer for Grand Rounds, Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation	

- Hospital, Boston, MA
- January 29, 2014 Clinical Presentation and Diagnosis of Chronic Traumatic Encephalopathy: What We Think We Know and What We Need to Know Next, Invited Lecture, C4CT Summit, United Nations, New York, NY
- January 30, 2014 Brain Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma, Visiting Speaker, Mayo Clinic, Scottsdale, AZ
- March 19-23, 2014 Chronic Traumatic Encephalopathy, Invited Symposium Organizer and Speaker, 10th World Congress on Brain Injury, San Francisco, CA

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March 28, 2014	Head Games: Chronic Traumatic Encephalopathy and the Long-Term Consequences of Repetitive Brain Trauma in Athletes, Invited Speaker, Grand Rounds, Department of Medicine, Tufts Medical School, Boston, MA	
April 16-17, 2014	Chronic Traumatic Encephalopathy Clinical Presentation and Biomarkers: What We Know and What We Do Not Know, Invited Speaker, 4 rd Traumatic Brain Injury Conference, Washington, DC	
May 2, 2014	Chronic Traumatic Encephalopathy: What We Think We Know and What We Need to Know, Plenary Speaker, 8 th Annual National Summit on Sports Concussion, Los Angeles, CA	
May 13, 2014	Brain Games: Chronic Traumatic Encephalopathy and the Long Term Consequences of Repetitive Concussive and Subconcussive Brain Trauma in Athletes. Keynote Speaker, NYC MedTech Program, New York, NY	
May 30, 2014	Chronic Traumatic Encephalopathy, Invited Speaker, "Dementia: A Comprehensive Update" Continuing Medical Education Course, Harvard Medical School, Boston, MA.	
June 30, 2014	Overview of recent/current research in clinical endpoint development, "Pre-Dementia Clinical Outcome Assessment Tool (pCOA) Stage 2 Meeting, Coalition Against Major Diseases, Bethesda, MD	
July 31, 2014	Brain Trauma Leading to Alzheimer's Disease and Chronic Traumatic Encephalopathy: What We Know and What We Need to Know, Invited Lecture, C4CT Summit, United Nations, New York, NY	
November 12, 2014	Brain Games: What We Now Know and What We Must Know Next about Chronic Traumatic Encephalopathy, Opening Keynote Address, 2014 Annual Conference of the National Academy of Neuropsychology, Puerto Rico.	
MEDIA EXPERIENCE AND APPEARANCES:		

MEDIA EXPERIENCE AND APPEARANCES:

Fleishman-Hillard International Communications, New York, February 2009

Media Training:

Print Media:	Interviewed and quoted in national and international newspapers and news magazines, including the New York Times, Washington Post, Boston Globe, LA Times, Time Magazine, USA Today, and others.
Broadcast Media:	Interviews on ABC World News Tonight, CBS Evening News, NBC Nightly News, Good Morning America, Nightline, CNN, Fox News, National Public Radio, ESPN, CTV's Canada AM, ABC Radio Australia, ABC TV Australia, and numerous local affiliate radio and television news interviews.
Documentaries:	Appeared in Feature Length Film Documentary, "I Remember Better When I Paint"

Appeared in Feature Length Film Documentary, "I Remember Better When I Paint" (2009), French Connection Films and the Hilgos Foundation.

Appeared in Feature Length Film Documentary, "Head Games" (2012), Variance Films, Directed by Steven James.

Appeared in Feature Length Television Documentary, "League of Denial" (2013), *Frontline*, Public Broadcasting System (PBS), Directed by Michael Kirk.

ORIGINAL, PEER REVIEWED ARTICLES:

(Past and present students, fellows, and other trainees italicized)

- 1. Elder, J.P., & **Stern, R.A.** (1986). The ABC's of adolescent smoking prevention: An environment and skills model. Health Education Quarterly, 13, 181-191.
- 2. Elder, J.P., **Stern, R.A.**, Anderson, M., Hovell, M.F., Molgaard, C.A., & Seidman, R. (1987). Contingency-based strategies for the prevention of alcohol, drugs, and tobacco use: Missing or unwanted components of adolescent health promotion? <u>Education and Treatment of Children</u>, 10, 30-47.
- 3. **Stern, R.A.**, Prochaska, J.O., Velicer, W.F., & Elder, J.P. (1987). Stages of adolescent smoking acquisition: Measurement and sample profiles. <u>Addictive Behaviors</u>, <u>12</u>, 319-329.
- 4. Elder, J.P., de Moor, C., Young, R.L., Wildey, M.B., Molgaard, C.A., Golbeck, A.L., Sallis, J.F., & Stern, R.A. (1990). Stages of adolescent tobacco-use acquisition. <u>Addictive Behaviors</u>, <u>15</u>, 449-454.
- 5. Simmons, R.B., **Stern, R.A.**, Teekhassaenee, C., & Kenyon, K.R. (1990). Elevated intraocular pressure following penetrating keratoplasty. <u>Transactions of the American Ophthalmological Society</u>, 87, 79-93.
- 6. Simmons, R.B., Shields, M.B., Blasini, M., Wilkerson, M., & **Stern, R.A.** (1991). A clinical evaluation of transscleral Neodymium: YAG cyclophotocoagulation with a contact lens. <u>American</u> Journal of Ophthalmology, 112, 671-677.
- 7. **Stern, R.A.**, & Bachman, D.L. (1991). Depressive symptoms following stroke. <u>American Journal of Psychiatry</u>, 148, 351-356.
- 8. **Stern, R.A.**, Nevels, C.T., Shelhorse, M.E., *Prohaska, M.L.*, Mason, G.A., & Prange, A.J., Jr. (1991). Antidepressant and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: Preliminary findings. Biological Psychiatry, 30, 623-627.
- 9. Keenan, P., **Stern, R.A.**, Janowsky, D.S., & Pedersen, C.A. (1992). Psychological aspects of premenstrual syndrome I: Cognition and memory. Psychoneuroendocrinology, 17, 179-187.
- 10. **Stern, R.A.**, *Singer, N.G., Silva, S.G.*, Rogers, H.J., Perkins, D.O., Hall, C.D., van der Horst, C.M., & Evans, D.L. (1992). Neurobehavioral functioning in a nonconfounded group of asymptomatic HIV seropositive homosexual men. <u>American Journal of Psychiatry</u>, 149, 1099-1102.
- 11. **Stern, R.A.**, van der Horst, C.M., Hooper, S.R., Bloodgood, K.M., & High, K.A. (1992). Zidovudine overdose in an asymptomatic HIV seropositive patient with hemophilia. Psychosomatics, 33, 454-457.
- 12. Girdler, S.S., Pedersen, C.A., **Stern, R.A.**, & Light, K.C. (1993). The menstrual cycle and premenstrual syndrome: Modifiers of cardiovascular reactivity in women. <u>Health Psychology</u>, <u>12</u>, 180-192.
- 13. Haggerty, J.J. Jr., **Stern, R.A.**, Mason, G.A., Beckwith, J., *Morey, C.E.*, & Prange, A.J. Jr. (1993). Subclinical hypothyroidism: A modifiable risk factor for depression. <u>American Journal of Psychiatry</u>, 150, 508-510.
- 14. Pedersen, C.A., **Stern, R.A.**, *Pate, J.*, Senger, M.A., Bowes, W.A., & Mason, G.A. (1993). Thyroid and adrenal measures during late pregnancy and the puerperium in women who have been major depressed or who become dysphoric postpartum. Journal of Affective Disorders, 29, 201-211.
- 15. Robertson, K.R., **Stern, R.A.**, Hall, C.D., Perkins, D.O., Wilkins, J.W., *Gortner, D.T.*, Donovan, M.K., Messenheimer, J.A., Whaley, R., & Evans, D.L. (1993). Vitamin B₁₂ deficiency and nervous system disease in HIV infection. <u>Archives of Neurology</u>, <u>50</u>, 807-811.
- 16. **Stern, R.A.**, *Steketee, M.S.*, Durr, A., Prange, A.J. Jr., & Golden, R.N. (1993). Combined use of thyroid hormone and ECT. Convulsive Therapy, 9, 285-292.

17. Perkins, D.O., **Stern, R.A.**, Golden, R.N., Murphy, C., *Naftalowitz*, *D.*, & Evans, D.L. (1994). Mood disorders in HIV infection: Prevalence and risk factors in a non-epicenter of the AIDS epidemic. <u>American Journal of Psychiatry</u>, 151, 233-236.

- 18. **Stern, R.A.** (1994). Neuropsychiatric and psychoneuroimmune aspects of HIV infection and AIDS. Advances, 10 (4), 28-31.
- 19. **Stern, R.A.**, *Singer, E.A., Duke, L.M., Singer, N.G., Morey, C.E., Daughtrey, E.W., &* Kaplan, E. (1994). The Boston Qualitative Scoring System for the Rey-Osterrieth Complex Figure: Description and interrater reliability. <u>The Clinical Neuropsychologist</u>, *8*, 309-322.
- 20. Echelman, D.A., **Stern, R.A.**, Shields, S.R., Simmons, R.B., & Shields, M.B. (1995). Variability of contact transscleral neodymium: YAG cyclophotocoagulation. <u>Investigative Ophthalmology & Visual Science</u>, <u>36</u>, 497-502.
- Evans, D.L., Leserman, J., Perkins, D.O., **Stern, R.A.**, Murphy, C., Tamul, K., Liao, D., van der Horst, C.M., Hall, C.D., Folds, J.D., Golden, R.N., & Petitto, J.M. (1995). Stress associated reductions of cytotoxic T lymphocytes and natural killer cells in asymptomatic human immunodeficiency virus infection. <u>American Journal of Psychiatry</u>, 152, 543-550.
- Perkins, D.O., Leserman, J., **Stern, R.A.**, *Baum, S.F.*, Liao, D., Golden, R.N., & Evans, D.L. (1995). Somatic symptoms and HIV-1 infection: Relationship to depressive symptoms and indicators of HIV disease. American Journal of Psychiatry, 152, 1776-1781.
- 23. *Prohaska, M.L.*, **Stern, R.A.**, *Steketee, M.C.*, & Prange, A.J. Jr. (1995). Lithium, thyroid hormones, and neuropsychological functioning: A review and hypothesis. <u>Depression</u>, <u>2</u>, 241-251.
- 24. **Stern, R.A.**, *Whealin, J.M.*, Mason, G.A., Noonan, L.R., *Silva, S.G., Arruda, J.E.*, & Prange, A.J. Jr. (1995). Influence of L-triiodothyronine on memory following repeated electroconvulsive shock in rats: Implications for human electroconvulsive therapy. <u>Biological Psychiatry</u>, <u>37</u>, 198-201.
- 25. *Arruda, J.E.*, **Stern, R.A.**, & *Legendre, S.A.* (1996). Assessment of mood state in patients undergoing electroconvulsive therapy: The utility of Visual Analogue Mood Scales developed for cognitively-impaired patients. <u>Convulsive Therapy</u>, 12, 207-212.
- 26. *Arruda, J.E.*, Weiler, M.D., Valentino, D.S., Willis, W.G., Rossi, J.S., **Stern, R.A.**, Gold, S.G., & Costa, L. (1996). A guide for applying principal components analysis and confirmatory factor analysis to quantitative electroencephalogram data. <u>International Journal of Psychophysiology</u>, 23, 63-81.
- 27. *Cahn, D.A.*., Marcotte, A.C., **Stern, R.A.**, *Arruda, J.E.*, Akshoomoff, N.A., & *Leshko, I.C.* (1996). The Boston Qualitative Scoring System for the Rey-Osterrieth Complex Figure: A study of children with Attention Deficit Hyperactivity Disorder. The Clinical Neuropsychologist, 10, 397-406.
- 28. *Prohaska, M.L.* **Stern, R.A.**, Nevels, C.T., Mason, G.A., & Prange, A.J. Jr. (1996). The relationship between thyroid status and neuropsychological performance in psychiatric outpatients maintained on lithium. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 9, 30-34.
- 29. **Stern, R.A.**, *Robinson, B., Thorner, A.R., Arruda, J.E., Prohaska, M.L.*, & Prange, A.J. Jr. (1996). A survey study of neuropsychiatric complaints in patients with Graves' disease. <u>Journal of Neuropsychiatry and Clinical Neurosciences</u>, 8, 181-185.
- 30. **Stern, R.A.**, *Silva, S.G., Chaisson, N.*, & Evans, D.L. (1996). Influence of cognitive reserve on neuropsychological functioning in asymptomatic Human Immunodeficiency Virus-1 infection. Archives of Neurology, 53, 148-153.
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CASE REPORTS, REVIEWS, CHAPTERS, EDITORIALS AND OTHER PUBLICATIONS

Proceedings of Meetings & Invited Papers

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CV: Robert A. Stern, Ph.D.

Textbook Chapters

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Letters and Other Publications

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- 2. Tremont, G., & **Stern, R.A.** (2001). Minimizing the cognitive effects of lithium therapy and electroconvulsive therapy using thyroid hormone. .<u>Biologine Psichiatrija ir Psichofarmakologija</u> (Lithuanian journal; "Biological Psychiatry and Psychopharmacology"), 3, 5-11.
- 3. **Stern, R.A.**, Gavett, B.E., *Baugh, C.*, Nowinski, C.J., Cantu, R.C., & McKee, A.C. (2011). Recurrent Sports-Related Traumatic Brain Injury and Tauopathy. In <u>Nutrition and Traumatic Brain Injury: Improving Acute and Subacute Health Outcomes in Military Personnel</u>, edited by J. Erdman, M. Oria, and L. Pillsbury. Washington, DC: The National Academies Press. pp. 305-310.

Published Tests, Instruments, and Manuals:

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- 2. **Stern, R.A.**, *Javorsky, D.J., Singer, E.A., Singer, N.G., Duke, L.M., Somerville, J.A.*, Thompson, J.A., & Kaplan, E. (1999). <u>Boston Qualitative Scoring System (BQSS) for the Rey-Osterrieth Complex Figure, Psychological Assessment Resources (PAR), Odessa, FL.</u>
- 3. **Stern, R.A.** & White, T. (2003). <u>Neuropsychological Assessment Battery (NAB)</u>, Psychological Assessment Resources (PAR), Lutz, FL.

In addition to the entire battery, the following individual tests and modules are available from the publisher:

NAB Screening Module

NAB Attention Module

NAB Language Module

NAB Memory Module

NAB Spatial Module

NAB Executive Functions Module

NAB Auditory Comprehension Test

NAB Categories Test

NAB Design Construction Test

NAB Digits Forward/Digits Backward Test

NAB Mazes Test

NAB Naming Test

NAB Numbers and Letters Test

NAB Orientation Test

NAB Visual Discrimination Test

NAB Writing Test

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- 8. Mohyde, M., Tracton-Bishop, B., Coughlin, J. D'Ambrosio, L., & **Stern, R.A**. (2007). <u>At the Crossroads: The Support Group Kit on Alzheimer's Disease, Dementia & Driving</u>. The Hartford, Hartford, CT.

The kit was developed collaboratively by BU School of Medicine, MIT AgeLab, The Hartford Financial Services Group the three organizations, based on materials developed for a research study (**PI R. Stern**) of dementia caregivers and driving. Other major contributors include from the MIT AgeLab. The support group kit was the recipient of a *Today's Caregiver* Magazine's "2011 Caregiver Friendly" Award.

UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated,

Plaintiffs,

V.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cv-00029-AB

DECLARATION OF SEAN MOREY

Pursuant to 28 U.S.C. § 1746, Sean Morey declares as follows:

- 1. I have ten credited seasons playing in the NFL, as a wide receiver and as a member of the special teams.
- 2. I began my NFL career in 1999 with the New England Patriots. I played for the Philadelphia Eagles in 2002, and throughout the 2003 NFL season. I played for the three seasons with the Pittsburgh Steelers in 2004, 2005 & 2006. I played the final three seasons of my NFL career with the Arizona Cardinals from 2007 until 2009. I retired in 2010.
- 3. I am also a veteran of NFL Europe. In 2000, the Patriots allocated me to the Barcelona Dragons where I played wide receiver and on special teams. I returned to the Dragons

for the 2001 season, allocated again by the New England Patriots to play defensive back and special teams. I was then allocated to the Barcelona Dragons by the Philadelphia Eagles in 2003, where I played my third and final season in NFL Europe.

- 4. During training camp for and throughout the three seasons that I played in NFL Europe, I suffered repeated head trauma.
- 5. The NFL Europe season lasted ten games with one additional championship game. Additionally, all teams would have live scrimmages during training camp in Florida, which lasted approximately two weeks before traveling to Europe for the season. In addition, some NFL Europe teams held "full contact" practices during the week throughout the season.
- 6. NFL Europe games were largely the same as NFL games played here in the United States. The field dimensions, duration of game, and principal rules were largely the same as those in the NFL. Unlike the NFL, however, NFL Europe restricted overload blitzes; as defenses were restricted in the number of rushers to a particular side. The rule sought to simplify protection schemes and protect quarterbacks. Otherwise, the rules governing contact were largely the same as those in the NFL.
- 7. The NFL Europe season did not overlap with the NFL season. Thus, some players played a full season in NFL Europe, went directly into NFL Training Camps, and played an entire season in the NFL in a single year. In 2003, for example, I played 33 games total: 10 games with the Dragons in NFL Europe and 23 games with the Eagles in the NFL (4 preseason games, 16 regular season games, and 3 playoff games).
- 8. NFL Europe was not equipped to provide the level of medical care necessary for injured football players. I found it difficult to communicate with the foreign doctors, who often did not speak English, and the athletic trainers were ill-equipped and often inexperienced. NFL

Europe did not have a neurological expert on the sideline and did not implement any concussion protocol.

9. I am aware that, from time to time, players playing in NFL Europe were flown to Health South in Birmingham, Alabama for medical care as a result of those players not being able to receive appropriate care in Europe, as well as for rehabilitation.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: October 6, 2014

Sean Moter

UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated.

Plaintiffs,

V.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cv-00029-AB

MOTION OF SEAN MOREY, ALAN FANECA, BEN HAMILTON, ROBERT ROYAL, RODERICK CARTWRIGHT, JEFF ROHRER, AND SEAN CONSIDINE FOR LEAVE TO FILE A REPLY IN SUPPORT OF MDL DOCKET NO. 6169 (MOTION FOR LEAVE TO CONDUCT LIMITED DISCOVERY)

For the reasons set forth in the accompanying Memorandum of Law and pursuant to Paragraph 2 of the Court's General Motion Practices, Sean Morey, Alan Faneca, Ben Hamilton, Robert Royal, Roderick "Rock" Cartwright, Jeff Rohrer, and Sean Considine (the "Movants") respectfully move for leave to file a reply in support of Docket No. 6169, Movants' September 13, 2014 motion for leave to conduct limited discovery. A proposed reply memorandum is attached as Exhibit A.

WHEREFORE, for the reasons stated above and in the accompanying Memorandum of Law, Sean Morey, Alan Faneca, Ben Hamilton, Robert Royal, Roderick Cartwright, Jeff Rohrer, and Sean Considine respectfully request that this Court enter an order granting them leave to file a reply memorandum in support of their motion for limited discovery.

Dated: October 13, 2014

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/s/ Steven F. Molo

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Attorneys for Movants

CERTIFICATE OF SERVICE

I hereby certify that on October 13, 2014, I caused the foregoing Motion for Leave to File Reply Brief, Memorandum of Law, Proposed Reply, and Proposed Order to be filed with the United States District Court for the Eastern District of Pennsylvania via the Court's CM/ECF system, which will provide electronic notice to all counsel and parties.

/s/ Steven F. Molo

UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated.

Plaintiffs,

V.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cv-00029-AB

MEMORANDUM OF LAW IN SUPPORT OF MOVANTS' MOTION FOR LEAVE TO FILE A REPLY IN SUPPORT OF MDL DOCKET NO. 6169 (MOTION FOR LEAVE TO CONDUCT LIMITED DISCOVERY)

On September 13, 2014, Movants filed a motion for leave to conduct limited discovery for purposes of preparing for this Court's November 19, 2014 fairness hearing. Dkt. No. 6169. On October 2, 2014, the NFL and Class Counsel filed oppositions. Dkt. Nos. 6183, 6185.

Movants respectfully request leave to file a reply memorandum so that Movants may respond to and rebut the contentions raised in the oppositions to Movants' Motion for Leave to Conduct Limited Discovery. A reply is necessary because of the importance of the matter and to correct the misstatements of law and fact in Class Counsel's and the NFL's oppositions. The interests of justice therefore favor granting leave to file a reply. Movants' request for leave to

file a reply memorandum is also timely because it will not delay the Court's consideration of any pending motion and because it is filed within eight business days after the oppositions were filed.

Dated: October 13, 2014

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Attorneys for Movants

UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated.

Plaintiffs,

V.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cv-00029-AB

SUPPLEMENT TO OCTOBER 6, 2014 OBJECTION OF SEAN MOREY, ALAN FANECA, BEN HAMILTON, ROBERT ROYAL, RODERICK CARTWRIGHT, JEFF ROHRER, AND SEAN CONSIDINE

Sean Morey, Alan Faneca, Ben Hamilton, Robert Royal, Roderick Cartwright, Jeff Rohrer, and Sean Considine (collectively, "Objectors") submit the Declaration of Samuel Gandy, M.D., Ph.D. ("Gandy Decl.") in further support of their Objection filed on October 6, 2014, MDL Dkt. No. 6201 ("Objection").

Dr. Gandy is Professor of Alzheimer's Disease Research and Professor of Neurology and Psychiatry at Mt. Sinai School of Medicine in New York City. He is also the Associate Director of the Mount Sinai Alzheimer's Disease Research Center and Chairman Emeritus of the National Medical and Scientific Advisory Council of the Alzheimer's Association. Dr. Gandy received

both his M.D. and his Ph.D. from the Medical University of South Carolina. Dr. Gandy's *curriculum vitae* is attached to his declaration.

The declaration of this prominent researcher further demonstrates that the Settlement is not fair, adequate, and reasonable. The Settlement fails to compensate players who die with CTE after July 7, 2014 while awarding \$4 million to the families of players who died with CTE before that date. As Co-Lead Class Counsel has admitted, "CTE is believed to be the most serious and harmful disease that results from NFL and concussions." Objection 2 & n.1. Yet, the rights of class members with CTE were bargained away without adequate representation.

As Dr. Gandy explains, CTE results in mood and behavioral disorders that are "serious and devastating." Gandy Decl. ¶ 5. These symptoms include "poor impulse control" and "socially inappropriate, avolitional, and apathetic behaviors" as well as "impulsivity, aggression," and "'short fuse' explosive behaviors." Gandy Decl. ¶ 6. CTE's behavioral and mood symptoms are not compensated under the Settlement, however, in that class members receive no

Frequent brain trauma or multiple football concussions . . . has shown to cause serious mental health problems. Thousands of football players, many of whom are thought to have suffered more than one hundred mild traumatic brain injuries, are dealing with horrible and debilitating symptoms.

Multiple medical studies have found direct correlation between football concussions and suffering from symptoms of chronic traumatic encephalopathy, also known as CTE. *CTE* is believed to be the most serious and harmful disease that results from NFL and concussions. CTE is a progressive degenerative disease that causes damage to the brain tissue and the accumulation of Tau Proteins.

Up-To-Date Information on NFL Concussions, Seeger Weiss LLP, (Sept. 9, 2014), http://www.seegerweiss.com/football-concussions/#ixzz3CByVHxui (emphasis added) (Objection 2 n.1 & Ex. 1). Seeger Weiss quickly removed that language after oral argument in the Third Circuit on September 10, 2014, at which the inadequate representation and failure to compensate CTE, as well as this language on their website, was raised.

¹ Co-Lead Class Counsel Seeger Weiss used to have on its website a tutorial relating to MTBI and football:

compensation for future cases of CTE and because the behavioral and mood symptoms do not qualify for payment under any of the other qualifying diseases. Objection 21-32, 69-70 & n.83.

CTE typically presents in younger individuals when compared to other neurodegenerative conditions, like those that qualify for payment under the settlement (ALS, Parkinson's, Alzheimer's, and dementia). Gandy Decl. ¶ 7. Thus, individuals with CTE are left to cope with "decades of disability." *Id.* That is particularly true of CTE's mood and behavioral symptoms, which typically present in mid-life. *Id.* Thus, compensating CTE-related neurocognitive decline as Level 1.5 or Level 2.0 dementia is inadequate – it would leave many class members afflicted with CTE to suffer years or decades of CTE's mood and behavioral symptoms before becoming eligible to participate in the Settlement. Objection 28-30. Many individuals with CTE, moreover, never develop dementia: "The high rates of suicides, accidents, and drug overdoses often lead to death before the individual reaches age 65," which is the age at which individuals with CTE might develop dementia. Gandy Decl. ¶¶ 8-9. For those individuals, the Settlement offers *nothing*. *See* Objection 28-29.

The Settlement's testing protocols are also insufficient. Although CTE is currently not amenable to a reliable, definitive diagnosis in living persons, there are recommended testing protocols for individuals suspected to have CTE. That recommended testing includes "neuropsychological evaluation, neurological examination, brain imaging, and blood and CSF biomarkers." Gandy Decl. ¶ 12. The testing provided by the Baseline Assessment Program, however, does not meet those requirements: It focuses only on cognitive function and lacks the neurological examination, brain imaging, and blood and CSF biomarker testing that should be included when screening for CTE. *Id.*; *see also* Objection 72-73. In any event, recent advances in diagnostic imaging technology have identified tracers that can spot the accumulation of brain

protein found in individuals suffering from CTE. Gandy Decl. ¶ 13. These tracers could soon allow for a more definitive diagnosis of CTE in a living person. *Id.* The Settlement, however, freezes science in place and does not account for such scientific advancements that aid physicians in identifying and treating CTE. Objection 26.

Dated: October 14, 2014

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Respectfully submitted,

/s/ Steven F. Molo

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Attorneys for Objectors

CERTIFICATE OF SERVICE

I hereby certify that on October 14, 2014, I caused the foregoing Supplement to October 6, 2014 Objection and supporting declaration to be filed with the United States District Court for the Eastern District of Pennsylvania via the Court's CM/ECF system, which will provide electronic notice to all counsel of record.

/s/ Steven F. Molo Steven F. Molo

UNITED STATES DISTRICT COURT EASTERN DISTRICT OF PENNSYLVANIA

IN RE: NATIONAL FOOTBALL LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

Kevin Turner and Shawn Wooden, on behalf of themselves and others similarly situated.

Plaintiffs,

V.

National Football League and NFL Properties, LLC, successor-in-interest to NFL Properties, Inc.,

Defendants.

THIS DOCUMENT RELATES TO: ALL ACTIONS

No. 2:12-md-02323-AB MDL No. 2323

Civil Action No. 2:14-cv-00029-AB

DECLARATION OF SAM GANDY, M.D., PH.D.

Sam Gandy, M.D., Ph.D., affirms under penalty of perjury the truth of the following facts:

- 1. I am the Mount Sinai Professor of Alzheimer's Disease Research, Professor of Neurology and Psychiatry, Associate Director of the Mount Sinai Alzheimer's Disease Research Center in New York City, and Chairman Emeritus of the National Medical and Scientific Advisory Council of the Alzheimer's Association.
- 2. My complete *curriculum vitae* is attached at Exhibit 1. Experience and training of particular relevance to this declaration includes certification by the American Board of Psychiatry and Neurology as a Diplomate in the specialty of Neurology and by my nomination and service as Official Delegate from the American Academy of Neurology as author and quality

assessor of items for the creation of new certification in Brain Injury Science by the American Board of Physical Medicine and Rehabilitation.

- 3. I have reviewed generally the Class Action Settlement Agreement as of June 25, 2014, together with its exhibits (the "Settlement"), filed in the above captioned proceeding, with particular attention to Exhibits 1 and 2 of the Settlement.
- 4. Pathologically, CTE involves build-up of phosphorylated tau protein in the brain. Higher levels of tau build-up are believed to associate with more advanced stages of CTE. CTE is the only neurodegenerative disease that has been linked to a specific acquired cause repeated head trauma. What sets CTE apart from other neurocognitive injuries is a relentlessly progressive course leading to a syndrome of psychological, mood, cognitive, and/or motor deficits that continue to progress even in the absence of further head trauma.
- 5. The primary clinical features of CTE include impairment of cognition, mood, behavior and/or movement. Individuals with neuropathologically confirmed CTE have significant problems with mood, behavior, and/or movement and not just problems with cognition. These behavioral, mood, and movement disorders are serious and devastating; they are equally as important and can be equally as disabling as the cognitive disorders that can result from head impacts.
- 6. For example, these mood and behavioral symptoms include impairment of executive function, poor impulse control, socially inappropriate, avolitional, and apathetic behaviors. Damage to the orbitofrontal regions of the brain can result in significant personality changes, including apathy, impulsivity, aggression, and the "short fuse" explosive behaviors that are typical of CTE as the illness is known based on neuropathological indexing. Such personality changes are consistent with the atrophy and other neuropathological changes of the

frontal lobes that have been described in nearly all reported cases of CTE. These mood and behavioral symptoms can have a devastating impact on an individual's life.

- 7. These mood and behavioral symptoms of CTE typically present in mid-life after a latency period as long as years or decades after the exposure. Because CTE symptoms present much earlier than the symptoms of other neurodegenerative diseases, individuals with CTE face decades of disability, a challenge that others afflicted with neurodegenerative disease do not face.
- 8. As CTE progresses, individuals with CTE develop worsening memory impairment, language problems, motor dysfunction, and continued aggression. Dementia is evident in most individuals with CTE who survive to age 65.
- 9. Some patients with CTE, however, may never reach dementia. The high rates of suicides, accidents, and drug overdoses often lead to death before the individual reaches age 65. Thus, many persons with neuropathologically confirmed CTE do not have dementia at time of death.
- 10. Other cases of CTE may never advance past the mood and behavioral changes that are typical of how CTE first presents, at least in CTE as identified in neuropathological series. Even for those individuals whose CTE does not progress to dementia, the impact of CTE on a patient's ability to regulate his mood and behavior prior to ever reaching dementia can be devastating and totally incapacitating. For example, based on statements by family members that are published in the public domain, it is not clear that either Junior Seau and Dave Duerson would have qualified for dementia payments under the settlement. Both are former NFL players who displayed hallmark characteristics of CTE's mood and behavioral symptoms hopelessness,

aggression, and poor impulse control. Both eventually committed suicide and were found to have CTE.

- 11. The Settlement does not compensate these mood, behavioral, or motor symptoms of CTE.
- 12. Although a definitive diagnosis of CTE in the living is currently beyond the reach of present medical technology, there are recommended diagnostic protocols for individuals who may have CTE. That recommended assessment includes neuropsychological evaluation, neurological examination, brain imaging, and blood and CSF biomarkers. Particular attention should be paid to cognitive function, mood, personality, behavior, and olfaction. The Settlement's testing protocol, however, does not meet this recommendation. It lacks neurological examination, brain imaging, and blood and CSF biomarker testing. It focuses only on cognitive function, not mood, personality, behavior, and olfaction.
- 13. Recent developments in medical diagnostic imaging technology, moreover, are moving toward giving physicians the ability to detect and diagnose CTE in living people. For example, PET tracers are available that bind to tau protein in the brain. Those tracers can then be highlighted using standard imaging technology, such as a PET scan. Combining those tau tracers with beta amyloid tracers can enable the clinician to distinguish between CTE and Alzheimer's. An Alzheimer's patient will show build-up of both substances, while most CTE patients will show only tau build-up.
- 14. Indeed, a research group in which I participated recently reported on the ability to use such PET tracers in a published, peer-reviewed paper. That study used both tau and beta amyloid tracers to study two individuals, one of whom was suspected of having Alzheimer's. The distribution of tau and beta amyloid, however, was more indicative of CTE than

Alzheimer's. The clinical misdiagnosis of CTE as Alzheimer's is not unusual. As research

continues on these technologies, such tracers will become more sensitive, more accurate, and

CTE diagnoses in living people will become more reliable.

15. CTE is a distinct, neurodegenerative disease. It is different from other

neurodegenerative diseases, such as those that qualify for payment under the Settlement. For

example, the neuropathology of a brain with Alzheimer's is different than that of a brain with

CTE. Both brains show tau tangles but they differ in the frequency of presence of amyloid

plaques. Yet all four of these diseases – Parkinson's, ALS, Alzheimer's, and CTE – can be

definitively determined through examination of brain tissue on autopsy following death. Using

currently approved technology, none of CTE, Alzheimer's, Parkinson's, or ALS can be

definitively diagnosed during life.

16. Dementia is neither a single illness nor a single disease. Instead, it is a descriptor

of a person's neurocognitive decline. Thus, some neurodegenerative diseases can lead to

dementia. Alzheimer's, CTE, and Parkinson's, and ALS are all such diseases. The brain

pathologies of these diseases begin well before any symptoms and well before the onset of

dementia. Only after the disease has destroyed enough brain tissue in clinically important brain

regions do the symptoms of dementia begin to present. Initial symptoms are not technically

"dementia." Only when the disease has sufficiently progressed that a person's cognitive decline

begins to interfere with independent functioning would an individual be characterized as having

dementia.

Pursuant to 28 U.S.C. § 1746, I state under penalty of perjury that the foregoing is true

Sam Gandy, M.D., Ph.D.

and correct:

Date: 09 Oct 2014

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EXHIBIT 1

Case 18-2012-mcDocuments 00311331-658032-Rage 19-690/140 Late Pitent 08/09/2019 April 6, 2014

CURRICULUM VITAE

Sam Gandy, M.D., Ph.D.

ACADEMIC APPOINTMENTS

2007- Present	Mount Sinai Professor of Alzheimer's Research Professor of Neurology and Psychiatry (Dual Primary) Icahn School of Medicine at Mount Sinai, New York, NY		
2001-2007	Paul C. Brucker, M.D., Professor of Neuroscience Professor of Neurology, Biochemistry and Molecular Biology Founding Director, Farber Institute for the Neurosciences Thomas Jefferson University, Philadelphia, PA		
1999-2000	Raine Foundation Visiting Distinguished Professor University of Western Australia, Perth WA, Australia		
1997-2001	Research Scientist The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY		
1997-2001	Professor of Psychiatry and Cell Biology New York University School of Medicine, New York, NY		
1997-Present	Adjunct Professor of Molecular and Cellular Neuroscience The Rockefeller University, New York NY		
1993-97	Associate Professor and Laboratory Director Department of Neurology and Neuroscience The New York Hospital Cornell Medical Center, New York, NY		
1993-97	Adjunct Associate Professor The Rockefeller University, New York, NY		
1992-93	Assistant Professor and Laboratory Director Department of Neurology and Neuroscience The New York Hospital-Cornell Medical Center, New York, NY		
1991-92	Assistant Professor, Laboratory of Molecular and Cellular Neuroscience The Rockefeller University, New York, NY		

HOSPITAL APPOINTMENTS

2011-Present	Director, Center for Cognitive Health and NFL Neurological Center Mount Sinai Hospital, New York NY
2007-Present	Attending Neurologist, Mount Sinai Hospital, New York, NY
2007-Present	Attending Neurologist James J. Peters Veterans Affairs Medical Center, Bronx, NY
2001-2007	Attending Neurologist Thomas Jefferson University Hospital, Philadelphia, PA

Cas@alse2012-mdD028111eAtB003111331e658232-Pageile9700/14D1ate Fitegel 98/09/2019 Gandy, Sam 2

1986-88: Attending Neurologist, The New York Hospital, New York, NY

General Neurology Clinic and Consult Service

1983-86: Resident and Clinical Associate in Neurology

The New York Hospital-Cornell Medical Center, New York, NY

1982-83: Intern, Department of Medicine, Presbyterian Hospital

Visiting Clinical Fellow, College of Physicians and Surgeons

Columbia University, Columbia-Presbyterian Medical Center, New York, NY

EDUCATION

1976: B.S., *summa cum laude*, Charleston Southern University (Chemistry)
1982: M.D., Ph.D., Medical University of South Carolina (Molecular Cell Biology)

POSTDOCTORAL TRAINING

1982-83: PGY 1 Intern, Columbia University College of Physicians and Surgeons,

Supervisor: John Bilizekian

1983-86: PGY 2-4 Resident in Neurology, Cornell University Medical College

Supervisor: Fred Plum

1986-91: Postdoctoral Research Associate, The Rockefeller University

Supervisor: Paul Greengard

CERTIFICATION

1988 Diplomate in Neurology, American Board of Psychiatry and Neurology

LICENSURE

7/1/1983 New York, License # 154552

2/8/2002 Pennsylvania, License # MD418573

7/13/2007 Georgia, License # 059726

HONORS/AWARDS/PATENTS

1976 B.S., summa cum laude1981 Alpha Omega Alpha

2008 Arthur Cherkin Memorial Award in Geriatric Medicine

University of California, Los Angeles

Issued Patents

5,385,915 Treatment of amyloidosis associated with Alzheimer disease using

modulators of protein phosphorylation

Issued: January 31, 1995

5,348,963 Method of screening for modulators of amyloid formation

Issued: September 20, 1994

5,242,932 Treatment of amyloidosis associated with Alzheimer disease

Issued: September 7, 1993

4,874,694 Use of phosphoprotein patterns for diagnosis of neurological and psychiatric

disorders; Issued: October 17,1989

OTHER PROFESSIONAL APPOINTMENTS

1. Committee Memberships

a. Regional and State:

Ad Hoc Pilot Proposal Reviewer, Alzheimer Disease Core Center, New York University, 1991-2000

b. Institutional:

Appointments and Promotions, Thomas Jefferson University Committee on Special Awards. Mount Sinai School of Medicine

2. Current consultancies

Baxter Pharmaceuticals Amicus Therapeutics Janssen/Pfizer Alzheimer's Initiative Diagenic

3. Editorships and Editorial Boards

Present

Associate Editor, *Alzheimer's Disease and Associated Disorders*, 1992-present Associate Editor, *Molecular Neurodegeneration*, 2005-present

Editorial Advisory Board, *Neurodegenerative Diseases*, 2003-present Editorial Board, *Journal of Neuroinflammation*, 2004-present Editorial Board, *Public Library of Science: Medicine*, 2007-present Member, Faculty of 1000 Biology, 2008-present Editorial board, *The Journal of Biological Chemistry*, 2012-present

Past

Consulting Editor, *The Journal of Clinical Investigation*, 2003-2013

ADMINISTRATIVE LEADERSHIP APPOINTMENTS

INTERNAL

1992-1997	Designer, Neurology and Neuroscience Problem Based Curriculum Weill Cornell Medical College
2001-2007	Founding Director, Farber Institute for Neurosciences Founder, Alzheimer's Clinical Trials Program, Jefferson Medical College
2007-present	Committee for Special Awards, Icahn School of Medicine at Mount Sinai Friedman Brain Institute, Faculty Search Committee

2007-present Chief, Division of Neurodegeneration, Friedman Brain Institute

EXTERNAL

National and International

1993-2009 1993-present	Ad Hoc IRG Member and Site Visitor, NINDS, NIA Ad Hoc Reviewer, The Wellcome Trust
1995-2001 1997-1998	Member, NIH, Neurological Sciences-1 Initial Review Group Chair, NIH, Neurological Sciences-1 Initial Review Group (Study Section)
2000-2006 2001-2006	Chair, Rotary Club CART Grant Award Committee Chair, Scientific Advisory Board, Elizabeth and Zachary Fisher
2001 2000	Foundation for Alzheimer's Research
2005-2009	Chair, Alzheimer's Association National Medical and Scientific Advisory Council

STUDENT TRAINING RECORD

NAME	LEVEL OF TRAINEE	ROLE IN TRAINING	TRAINING VENUE	TRAINEE'S CURRENT STATUS & INSTITUTION EMPLOYED
Gregg Caporaso	Ph.D. Student	Direct Supervision	Laboratory	Asst. Prof. Neurology, NYU
Joseph Buxbaum	Postdoctoral Fellow	Direct Supervision	Laboratory	Professor of Psychiatry, Mt. Sinai, NYC
Kerstin Iverfeldt	Postdoctoral Fellow	Direct Supervision	Laboratory	Professor, Chair, Neurochemistry, Stockholm University
Toshiharu Suzuki	Postdoctoral Fellow	Direct Supervision	Laboratory	Professor, Hokkaido University
Christer Nordstedt	Postdoctoral Fellow	Direct Supervision	Laboratory	VP Neuroscience, Astra Zeneca, Sodertalje, Sweden
Huaxi Xu	Postdoctoral Fellow	Direct Supervision	Laboratory	Professor, Burnham Institute
Suzana Petanceska	Postdoctoral Fellow	Direct Supervision	Laboratory	Program Officer, NIA

		1		
Parvathy Sarapavanavananthan (deceased)	Postdoctoral Fellow	Direct Supervision	Laboratory	Research Associate, UCSF, at the time of death
Ralph Martins	Postdoctoral Fellow	Direct Supervision	Laboratory	Professor, Edith Cowan University
Gunnar Gouras	Postdoctoral Fellow	Direct Supervision	Laboratory	Professor, Lund University
Jan Naslund	Postdoctoral Fellow	Direct Supervision	Laboratory	Staff Scientist, Astra Zeneca, Sodertalje, Sweden
Dun Sheng Yang	Postdoctoral Fellow	Direct Supervision	Laboratory	Research Associate, NKI
Jun Yao	Postdoctoral Fellow	Direct Supervision	Laboratory	Research Associate, Columbia University
Joshua Gatson	Postdoctoral Fellow	Direct Supervision	Laboratory	Postdoctoral Fellow, University of North Texas
Rachel Lane	Postdoctoral Fellow	Direct Supervision	Laboratory	Program Officer, ADDF
Soong Ho Kim	Postdoctoral Fellow	Direct Supervision	Laboratory	MSSM
Serene Keilani	Postdoctoral Fellow	Direct Supervision	Laboratory	Retired
Eugene Hone	Postdoctoral Fellow	Direct Supervision	Laboratory	Postdoctoral Fellow, Edith Cowan University
John Steele	Predoctoral Fellow	Direct Supervision	Laboratory	Postdoctoral Fellow, The Rockefeller University
Ina Caesar	Postdoctoral Fellow	Direct Supervision	Laboratory	Fellow, Linkoping University
Hannah Brautigam	Predoctoral Fellow	Direct Supervision	Laboratory	Undecided

Elysse Knight	Postdoctoral Fellow	Direct Supervision	Laboratory	MSSM	l
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DIDACTIC TEACHING ACTIVITIES

TEACHING ACTIVITY / TOPIC	LEVEL	ROLE	NUMBER OF LEARNERS	NUMBER OF HOURS PER WEEK / MONTH / YEAR	YEARS TAUGHT
Neurological Diagnosis	Medical School Course	Course Director and Lecturer	100	5 hr/wk 9 mo/year	1992-1995
Problem Based Approach to Basic and Clinical Sciences	Medical School Course	Neurology and Neuroscience Section Head and PBL Leader	100	5 hr/wk 9 mo/year	1995-1997
Molecular Basis of Neurological Disease Summer Course	Cold Spring Harbor Laboratory: Sub-specialty course	Course Director and Speaker	25	18 hr/day 6 days/yr	1996-2006
Neuropsychiatric Research Course	Department of Psychiatry: Postgraduate Course	Course Director	25	5 hr/wk 3 mo/year	1997-2001
Scientific Foundations of Clinical Medicine	Medical School Course	Course Director and Lecturer, Dementia Module	100	5 hr/wk 3 mo/year	2001-2007

	ROLE IN PROJECT	DATES	DIRECT
FUNDING SOURCE, PROJECT TITLE & NUMBER	KOLL IN PROJECT	Gandy,	SEOSTS
NINDS 5 K08 NS001095	PI	7/1/86-6/30/91	\$80,000/Yr
Characterization of a Neuron-specific phosphoprotein		77 1700 0700701	5 Years
NIA Pilot Project	PI	1990-1992	\$50,000/Yr
Neuron-Specific Phosphoproteins in Alzheimer			2 Years
CSF			
NIA 5 P01 AG010491	Program Co-	1991-1996	\$900,000/Yr
Interdisciplinary Approach to Alzheimer Drug	Director		, ,
Discovery			
NIA 5 P01 AG010491	Project Leader	1991-1996	\$150,000/Yr
Cell Biology of Amyloid Precursor Protein Processing			
in vitro, in vivo			
NIA 5 R01 AG011508	PI	1992-1997	\$120,000/Yr
Molecular Cell Biology of Alzheimer Amyloidogenesis			
NIA Pilot Project	PI	1993-1994	\$50,000/Yr
Leadership & Excellence in Alzheimer's Disease			
NIA ADRC P50 AG08702	Co-Project Leader	1994-1995	\$120,000/Yr
Signal Transduction and Amyloid in Alzheimer's			
Disease			
NIA R01 AG013780	PI	1996-2001	\$150,000/Yr
Regulated Cleavage of Amyloid Precursor: Molecular Basis			
NIA 5 P01 AG009464	Deputy Program	1990-2001	\$900,000/Yr
Signal Transduction and Alzheimer's Disease - Cell	Director	The Rockefeller	
Biological Studies		University	
NIA 5 P01 AG009464	Project Leader		\$150,000/Yr
Cell Biological Studies of Amyloid Precursor Protein			
NIA 5R01AG018237	PI	2002-2005	\$120,000/Yr
Neuroanatomy of GABA _A receptors in Alzheimer's			
Disease			
NIA 5R01AG008206	PI	2002-2005	\$120,000/Yr
Neurotransmitter Anatomy in Alzheimer's Disease			
NINDS R01 NS41017	PI	2000-2007	\$706,500
"Estrogen Modulation of Brain Abeta Metabolism in			
<u>vivo"</u>			
Cure Alzheimer's Fund	PI	11/01/07 - 10/31/09	\$100,000
"Mouse Model of Intraneuronal and Vascular Abeta			
Oligomers"			
NIA R01 AG023611	PI	7/1/05 - 06/30/10	\$828,833
"Presenilin Domains and Reconstitution of Catalysis"			

FUNDING SOURCE,	ROLE IN PROJECT	DATES	DIRECT	SUPPLEMENTAL
PROJECT TITLE &			COSTS/YR	INFO
NUMBER				
NIA P01 AG010491 "Interdisciplinary Approach to Alzheimer Drug Discovery"	Director	9/30/05-8/31/12	\$977,663	Active
Cure Alzheimer's Fund "SorCS1, Diabetes, and Alzheimer's"	PI	4/1/11-3/31/12	\$100,000	Active; renewable
Amicus Pharmaceuticals	P!	9/1/10-12/31/12	\$100,000	Active, renewable
VA MERIT "Mouse Model of Intraneuronal Amyloid Beta Oligomerization"	PI	7/1/10 - 6/30/13	\$175,000	Active; renewable
NIA P50 AG005138 "Alzheimer's Disease Research Center"	Associate Director	5/1/97-3/31/15	\$200,381	Active; renewable
NINDS R01 "SorCS1, Diabetes, and Alzheimer's"	PI	1/1/12-12/31/15	\$1,200,000	Active; renewable
NIA R21 "Generation of Alzheimer's Brain Cells"	PI	7/1/12 - 6/30/14	\$175,000	Active; renewable
Cure Alzheimer's Fund "Foundation Grant for CAF Stem Cell Consortium"	PI	3/1/13 - 2/28/14	\$100,000	Active; renewable
Baxter Pharmaceuticals "Effect of Gammagard Liquid on Oligomer-Only Mouse Model"	PI	7/1/12 - 6/30/14	\$200,000	Active; renewable

Louis B. Mayer Foundation	PI	3/1/12 - 12/31/13	\$25,000	Active; renewable
Constellation Wines	PI	3/1/12 - 2/28/14	\$230,000	Active; renewable
NIA R01 "Integrative Approach to Alzheimer's Disease Complexity"	Multi PI	09/01/13 - 08/31/18	\$200,000	Active; renewable

PUBLICATIONS

Peer Reviewed Original Contributions

- 1. Bonnette, A.K. and *Gandy*, S. Isotopic exchange in Prussian blue. J. Chemical Education 1981; 58:355-357.
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- 5. Murray, G.J., Youle, R.J., *Gandy*, S.E., Zirzow, G.C. and Barranger, J.A. Purification of ß-glucocerebrosidase by preparative scale HPLC: The use of ethylene glycol containing buffers for chromatography of hydrophobic glycoprotein enzymes. Anal. Biochem. 1984; 147:301-310.
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- 9. *Gandy*, S.E. and Payne, R. Back pain in the elderly: updated diagnosis and management. Geriatrics 1986; 41(12): 59-62, 67-74.
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- 11. **Gandy**, S.E. and Heier, L.A. Clinical features and magnetic resonance images of primary intracranial arachnoid cysts. Ann. Neurol. 1987; 21:342-348.
- 12. Feldmann, E., *Gandy*, S.E., Becker, R., Zimmerman, R., Thaler, H.T., Posner, J.B. and Plum, F. Magnetic resonance imaging demonstrates descending transtentorial herniation. Neurology 1988; 38: 697-701.
- 13. **Gandy**, S., Czernik, A., and Greengard, P. Phosphorylation of Alzheimer disease amyloid precursor peptide by protein kinase C and Ca+2/calmodulin-dependent protein

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